Ascertaining Barriers for Compliance: policies for safe, effective and cost-effective use of medicines in Europe

Final Report of the ABC Project (Deliverable 7.1)

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1.1Introduction

This final report, part of the FP-7 funded ABC project 'Ascertaining Barriers to Compliance: policies for safe, effective and cost-effective use of medicines in Europe' (HEALTH-2007-3.1-5: Better use of medicines), aims to present research evidence to contribute to our knowledge about the nature, causes, consequences and policy responses to medication non-adherence. In so doing we hope to achieve our overarching aim of supporting policies for safe and cost-effective use of medicines in Europe.

Non-adherence to medicines is a global issue of major public health concern. Non-adherence to medication is a frequent and widespread phenomenon, can be a major barrier for realising the benefits of medicines presents and is a significant barrier to the safe, effective and cost-effective use of medicines. Many patients do not adhere to effective treatments for the preservation of life[1,2], quality of life[3-5], organs[6], or sight[7,8], with direct clinical[9,10] and economic consequences[11,12].

Non-adherence is recognised as one of the major factors contributing to therapeutic partial or non-response[13,14]. It is highly prevalent, associated with increased morbidity and mortality, costly to manage, and until recently a very much neglected aspect of prevention and treatment of illness[13,14,15]. A report by the World Health Organisation[13] has called non-adherence "a worldwide problem of striking magnitude". Indeed, R. Haynes goes further and states, 'increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments'[17]. This problem is especially relevant to European Union countries, where access to healthcare services is good and their utilisation is high. In such circumstances, further improvement in the effectiveness of medication cannot be realised without addressing patient non-adherence.

In 2007 when the ABC Project was conceived, world pharmaceutical market growth was estimated to be 5-6%, and global pharmaceutical sales were estimated to reach $665-685 billion (www.imshealth.com). In 2007, each European citizen spent on average approximately € 430 on medicines. In total, the market for medicines was worth over € 138 billion at ex factory prices and approximately € 214 billion at retail prices, corresponding to 2% of the GDP[18]. Pharmaceutical expenditure is the third largest component of health expenditure, following hospital and ambulatory care spending, among EU member states[19].

In the past decade there has been substantial growth in adherence research – partly owing to increasing awareness of the size and scope of the problem, partly because of the pervasiveness of non-adherence across all therapeutic fields, and partly because of its potentially large contribution to the overall variance in drug responses. The medication adherence field is characterised by the lack of effective policies toward the problem of non-adherence at both national and European levels. Therefore, there is a need to produce evidence-based policy recommendations for European

policymakers in order to help both Europeans and European healthcare services improve patient adherence and make the most of available resources.

1.2 Overview of the ABC project

This final report of the ABC Project describes our work to investigate the following aims:

1. To obtain European consensus on terminology used in the field of non-adherence

Nowadays, a number of common terms – 'compliance', 'adherence', 'persistence', and 'concordance' - are used to define the act of seeking medical attention, filling prescriptions and taking medicines appropriately. These terms are sometimes used interchangeably, though they impose different views about the relationship between the patient and the health care professional. For example, the term 'compliance' has been criticised for its built-in paternalistic approach. Moreover, there is no consensus on a common definition on methods to measure ambulatory patients' exposure to prescribed drugs. The definitions that are currently used in the literature do not support quantitative assessment, thus compromising any sound analysis aimed at describing or comparing patients' adherence to prescribed drug dosing regimens. Those limitations preclude the finding of useful methods to enhance patient adherence with prescribed therapies in daily practice. Therefore, to allow for the benchmarking of existing adherence enhancing strategies at the European level, and support the preparation of policy recommendations, the starting point of the project was the clarification of existing terminology used in this field. Chapter 2 describes this part of the ABC Project.

2. To explore patient beliefs and behaviour regarding medication adherence.

This project takes an inventory of determinants of patient adherence described in the research literature, taking into account variation across different clinical sectors, health care settings and population segments. In addition, European surveys have been conducted to explore patients' beliefs and behaviour about their medicines and medicines taking behaviour. Further a discrete choice experiment is reported which investigates how participants weigh up the different attributes and outcomes of medicine taking which influence their potential treatment choices. Chapter 3 describes components of the ABC Project which explore patient beliefs and behaviour. Chapter 4 describes the integration of health psychology and economic models of patient behaviour that may be used to explain medication adherence. Systematic reviews were conducted to consolidate evidence into a new conceptual framework of determinants of medication adherence.

3. To obtain insight in current practices of adherence management by healthcare professionals, health educators and the pharmaceutical industry

Patient non-adherence is a frequent phenomenon in everyday clinical practice. Little is known about how healthcare professionals approach patient adherence and their reasons for choosing to intervene to support patients with medication adherence or not[20]. Equally, little is known about the ways in which educators prepare and provide continuing support to healthcare professionals to manage medication education. We are unaware of any European level data about healthcare professional education.

Chapter 5 describes a number of studies to investigate the education that healthcare professionals receive about medication adherence, the interventions that healthcare professional report that they use to support patients with medicine taking, and the guidelines that exist to support clinical practice. The pharmaceutical industry is becoming an increasingly influential stakeholder in the provision of adherence support for patients. Chapter 5 also includes a survey of pharmaceutical industry perceptions about their role in supporting patients with adherence to medication.

4. To assess the effectiveness of adherence-enhancing interventions

Although a number of adherence-enhancing interventions have been tested in clinical settings, evidence suggests that no single intervention strategy is satisfactorily effective across all patients, conditions and settings. Even the most effective interventions did not lead to large improvements in adherence and health outcomes[21,22]. Several reviews[22-24] of interventions for enhancing adherence to medications have consistently highlighted methodological weaknesses in the study designs and methods used, often precluding quantification and permitting only qualitative assessments. In particular, there are major between-study differences in methods used to assess adherence, differing not only in reliability but also in the degree of temporal resolution of their measurements. These methodological differences have thus hampered the identification of interventions that can effectively enhance adherence to medications. Chapter 6 presents a meta-analysis of intervention studies, focused only on those studies using electronic measurement of medicine-taking, to address this problem in the research evidence.

5. To estimate the cost-effectiveness of compliance-enhancing interventions

In order to develop strategies for successful policy recommendations that represent good value for money, and allow for effective benchmarking of existing European strategies, information about the cost-effectiveness of interventions aimed at enhancing patient adherence with both short-term and long-term treatments is key. A systematic review conducted by Elliott et al.[25] did not identify any robust economic evaluations, and the results of those that were included, were largely inconclusive. Chapter 7 presents an update of this review and an economic model, based on evidence from a systematic review of the literature, designed to estimate the cost-effectiveness of adherence-enhancing interventions in relation to antibiotics for adults with upper respiratory tract.

6. To develop policy recommendation for promoting patient adherence in European healthcare

Based on the activities listed above, the ABC Project developed policy recommendations for supporting patient adherence in order to assure safe, effective and cost-effective use of medicines in Europe. These are described in Chapter 8, alongside studies to develop consensus about policy solutions for medication adherence across Europe, and a key informant study of European policymakers' perceptions of the extent and adequacy of medication adherence policy implementation. Finally, a number of key multi-stakeholder dissemination events to share the learnings of the ABC Project are described.

1.3 Summary of objectives

Chapter 2

- to search the literature systematically, in order to identify the terms that have been used to describe medication-taking behavior, and to propose a new taxonomy, in which adherence to medications is conceptualized, based on behavioural and pharmacological science, and which will support quantifiable parameters.

Chapter 3

- To perform a systematic review to identify the determinants of patient compliance with short-term and long-term therapies in Europe
- To analyse the factors responsible for non-compliance with treatments for acute diseases, and chronic conditions for different clinical sectors, health care settings and population segments
- To identify the factors which influence patients' decisions in relation to the process of execution of short-term treatment and continuation with long-term treatments
- To quantify patients' preferences for a range of attributes relating to the decision-making process of being compliant or non-compliant

Chapter 4

- To draw from the health psychology, economics and clinical therapeutics literature, models of mediation adherence.
- To consolidate the evidence on the determinants of non-adherence in a conceptual framework of patient behaviour.
- To provide a theoretical basis for the development and assessment of adherence-enhancing interventions.
- To establish a basis for long-term behaviour modification for adherence with long-term therapies.
- To establish a basis for short-term behaviour modifications for adherence with treatments of acute diseases.

Chapter 5

- To evaluate whether pharmaceutical companies in Europe include medication adherence in their strategic plans.
- To evaluate what general methods pharmaceutical companies identify as ways in which they support medication adherence-enhancing interventions.
- To evaluate what specific interventions pharmaceutical companies report to be taking to improve patient adherence to prescribed medicines.
- To evaluate whether European high schools or universities of medicine, pharmacy, and nursing include medication adherence as a defined topic in their curricula.
- To evaluate what content is provided about medication adherence in health care professional training programs.

- To evaluate what specific methods European schools of medicine, pharmacy, and nursing use to educate future health care providers to address and improve patient adherence to prescribed medicines.
- To determine the methods that European healthcare professionals (medical doctors, nurses, pharmacists, etc.) currently use to support medication adherence.
- To determine what national and international medication adherence guidelines exist.
- To determine the characteristics of existing national- and international-level medication adherence guidelines.
- To determine what processes have been used to develop medication adherence guidelines.
- To determine how medication adherence guidelines have been distributed and where they have been published.

Chapter 6

- To systematically search the literature to identify randomized controlled trials containing empirical data on the efficacy of interventions to enhance adherence to prescribed medications, as assessed by electronic medication-event monitoring methods.

Chapter 7

- To update reviews of the literature associated with the cost-effectiveness of adherence-enhancing interventions.
- To estimate the economic impact of adherence-enhancing interventions using a decision analytic model populated by data from the literature review and other secondary sources.

Chapter 8

- To develop a common European educational framework specifying curriculum for schools of medicine, pharmacy and nursing for managing and supporting patients with medication adherence
- To reach consensus among medication adherence stakeholders on strategies to address patient adherence
- To develop policy recommendations for enhancing medication adherence in Europe
- To tailor medication adherence policy recommendations toward the needs of different healthcare settings and population segments, taking into account cultural differences between European regions.

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2 Consensus on European Taxonomy and Terminology of Patient Compliance

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2.1 Summary

Background: Interest in patient adherence has increased in recent years, with a growing literature that shows the pervasiveness of poor adherence to appropriately prescribed medications. However, four decades of adherence research has not resulted in uniformity in the terminology used to describe deviations from prescribed therapies.

Objectives: The objective of this research was to search the literature systematically, in order to identify the terms that have been used to describe medication-taking behavior, and to propose a new taxonomy, in which adherence to medications is conceptualized, based on behavioural and pharmacological science, and which will support quantifiable parameters.

Methods: A systematic literature review was performed using MEDLINE, EMBASE, CINAHL, the Cochrane Library and PsycINFO from database inception to 1 April 2009 in order to identify the different conceptual approaches to adherence research. Definitions were analysed according to time and methodological perspectives. A taxonomic approach was subsequently derived, evaluated, and discussed with international experts.

Results: More than ten different terms describing medication-taking behaviour were identified through the literature review, often with differing conceptual meanings. The conceptual foundation for a new, transparent taxonomy relies on three elements, which make a clear distinction between processes that describe actions through established routines ("Adherence to medications", "Management of adherence") and the discipline that studies those processes ("Adherence-related sciences"). "Adherence to medications" is the process by which patients take their medication as prescribed, further divided into three quantifiable phases: "Initiation", "Implementation", and "Discontinuation".

Conclusions: In response to the proliferation of ambiguous or unquantifiable terms in the literature on medication adherence, this research has resulted in a new conceptual foundation for a transparent taxonomy. The terms and definitions are focused on promoting consistency and quantification in terminology and methods to aid in the conduct, analysis, and interpretation of scientific studies of medication adherence.

2.2 Introduction

Sub-optimal adherence to prescribed medicines is frequently the principal obstacle to successful pharmacotherapy in ambulatory patients, especially when it is unrecognized clinically, as often occurs. It is highly prevalent, associated with increased morbidity and mortality, costly to manage, and until recently a very much neglected aspect of therapeutics[1-3.]

However, in the past decade there has been substantial growth in adherence research – partly owing to increasing awareness of the size and scope of the problem, partly because of the pervasiveness of non-adherence across all therapeutic fields, and partly because of its potentially large contribution to the overall variance in drug responses. Many patients do not adhere to effective treatments for the preservation of life[4;5], quality of life[6-8], organs[9], or sight[10;11], with direct clinical[12;13] and economic consequences[14;15].

Adherence research has also been spurred by: improved methods for compiling dosing histories in ambulatory patients, recognition of the importance of adherence to treatment outcomes in HIV-AIDS, increasing sizes of study populations, and lengthening periods of observation. However, this growth has been piecemeal, with research contributions coming from a variety of perspectives or academic disciplines. A predictable consequence has been an unsatisfactory taxonomic structure, leading to conceptual confusion[16-19].

Currently a number of terms – e.g. ‘compliance’, ‘adherence’, ‘persistence’, and ‘concordance’ – are used to define different aspects of the act of seeking medical attention, acquiring prescriptions, and taking medicines appropriately[20-37]. These terms are often used interchangeably, but they impose different views about the relationship between the patient and the health-care professional[38-40]. ‘Compliance’, for instance, has been viewed by many as having the negative connotation that patients are subservient to prescribers[41-45]. The term ‘concordance’, introduced originally to describe the patient-prescriber relationship, is sometimes incorrectly used as a synonym for ‘compliance’[46-57]. Most terms used currently do not have a clear or direct translation into different European languages[58]. These matters lead to confusion and misunderstanding, and impede comparisons of results of scientific research and implementation in practice[59;60].

2.3 Objectives

The objective of this work package was to search the literature systematically, in order to identify the terms that have been used to describe medication-taking behavior, and to propose a new taxonomy, in which adherence to medications is conceptualized, based on behavioural and pharmacological science, and which will support quantifiable parameters.

2.4 Methods

The first step consisted of a systematic literature review performed between January and June 2009. The objective was to assess the terms and definitions that are commonly used to describe adherence to medicines. We searched MEDLINE, EMBASE, CINAHL, the Cochrane Library, and PsycINFO from database inception to 1 April 2009 for all papers addressing the taxonomy/terminology used to describe deviations from prescribed drug treatment in ambulatory patients. The main search terms used were “Patient compliance” and “Medication adherence”. Because of the problem with translations, the searches were limited to papers in the English language. Detailed search strategies specific to the different databases are provided in Appendix 1.

Data extraction was undertaken by five independent reviewers (JD, FD, EF, CM, PL) using a structured data collection sheet to gather data on (a) publication type, (b) year of publication, (c) authors’ preferred terms for describing deviations from prescribed treatment, (d) authors’ proposed definitions, and (e) references cited in the paper. No additional information was sought from the authors.

A descriptive synthesis of the extracted data was performed and the historical development of the field was analysed. Based on the different conceptual approaches identified in the literature review, we derived an initial new taxonomic approach, which was first discussed internally within the ABC project team in June 2009 in Aberdeen, UK. The taxonomic approach was subsequently re-evaluated in light of the identified papers and refined in June-August 2009.

A European consensus meeting, attended by 80 participants from 13 different countries, was organized jointly with the European Society for Patient Adherence, Compliance and Persistence (ESPACOMP) in Bangor, Wales, UK on 10-11 September, 2009. During the meeting the draft consensus document was presented and extensively discussed. To broaden this discussion, an interactive wiki web-platform was opened during the last quarter of 2009.

In December 2009, a first report on the new taxonomy was submitted to the European Commission. In January 2010, an ABC internal consensus meeting was held in Sion, Switzerland. During that meeting, the strengths and weaknesses of the draft taxonomy were identified. From January 2010 until June 2010, the draft taxonomy was presented at different meetings and specific comments from experts were collected.

A final ABC internal consensus meeting took place in Leuven, Belgium in June 2010 for final approval of the taxonomy/terminology, which was subsequently presented at the 2010 ESPACOMP meeting held on 17-18 September in Lodz, Poland.

2.5 Results

2.5.1 Results from the literature review

Study selection

Figure 2.1 depicts the study selection process. Initial searching identified 3121 papers. 2975 original articles were excluded according to pre-defined exclusion criteria listed in Figure 2.1, resulting in 146 papers to review. The publication types were literature reviews (n=55), editorials/ commentaries/ letters/ discussions (n=34), theoretical papers/concept analyses (n=21), research papers (n=17), books (n=9), statistical papers (n=4), meeting reports (n=3), practice guidelines (n=2), and an expert report (n=1).

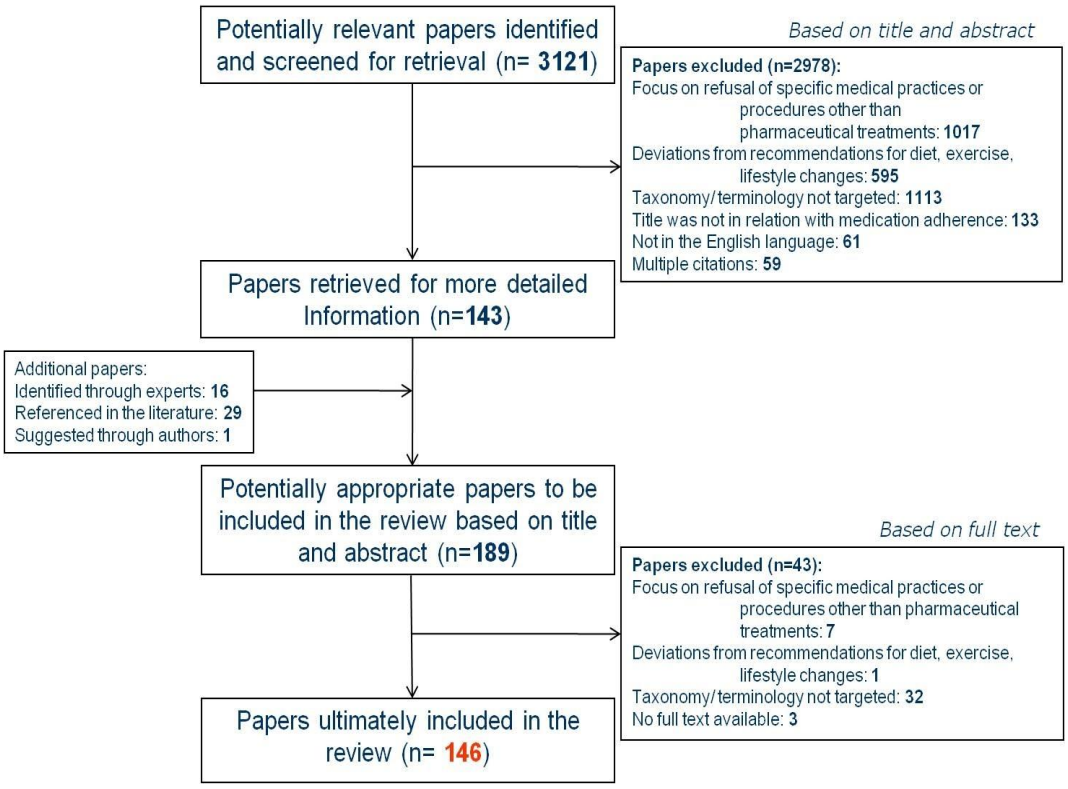

Fig 2.1

Flow diagram of the paper selection process

Terms identified

Figure 2.2 illustrates the many different terms describing deviations from prescribed treatment that have been introduced in the literature throughout the years. The data shown in this figure are incomplete for the year 2009, as papers were included up to 1 April 2009.

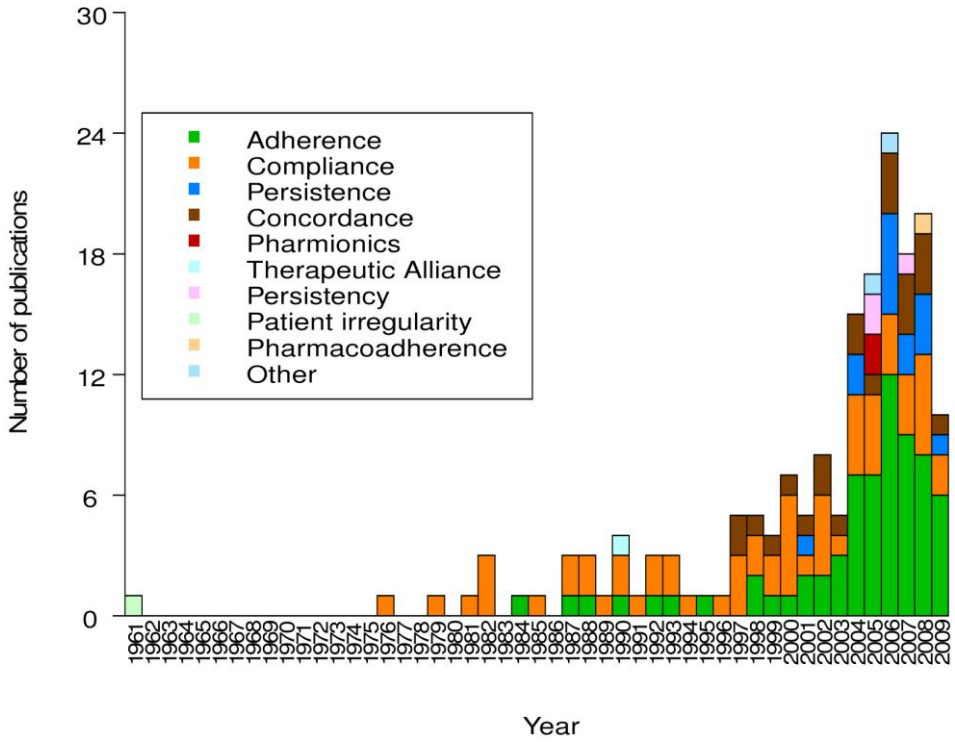

Fig 2.2

Frequency histogram presenting the evolution over time of the main terms used among the 146 papers to describe deviations from prescribed treatments

Since the pioneering research in this field, changes have occurred in prevailing philosophical paradigms and related concepts[61-63] as depicted in Figure 2.3.

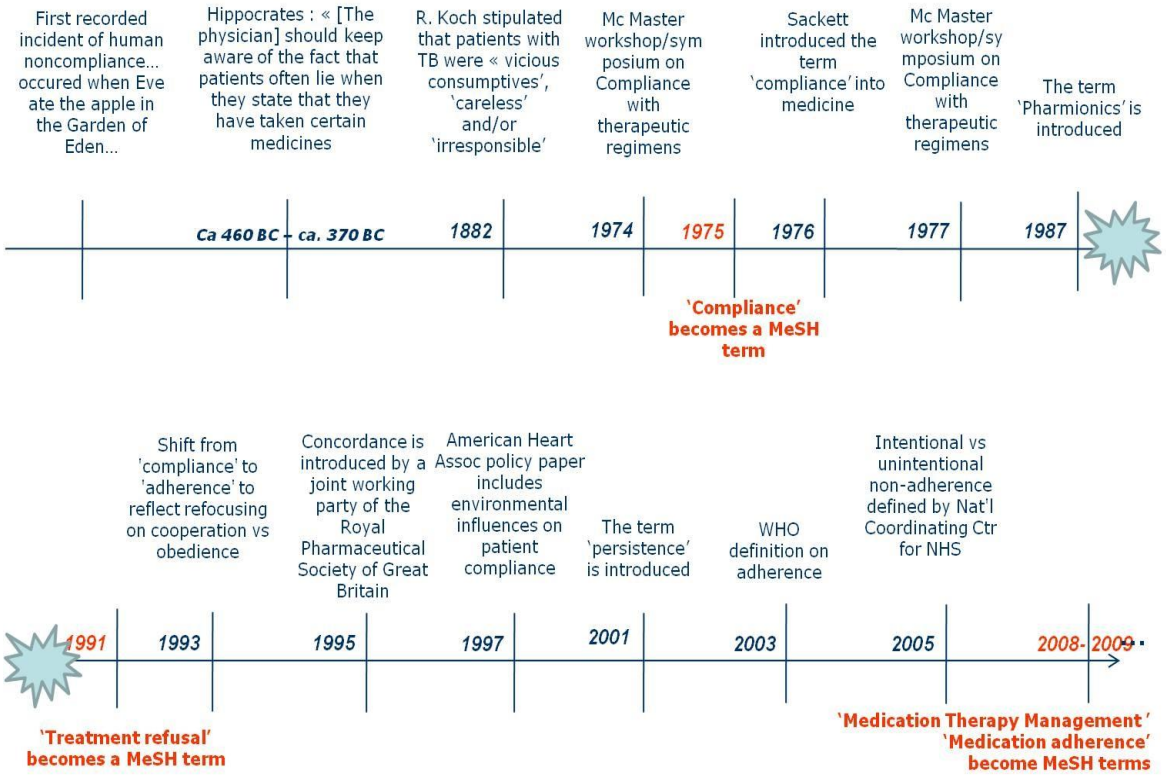

Fig 2.3

Time-line of changes in terminology for deviations from prescribed dosing regimens

Hippocrates (400 BC) was the first to note that some patients do not take their prescribed medicines, and that many later complained because the treatment didn't help. In 1882, for the first time in modern medicine, Robert Koch stipulated that noncompliant patients with tuberculosis were "vicious consumptives, careless, and/or irresponsible"[61].

Beginning in the 1970s, groundwork on patient compliance was initiated at McMaster University Medical Centre, resulting in two workshops/symposia and a seminal book entitled 'Compliance with Therapeutic Regimens' by Sackett and Haynes[64]. This initial research was triggered by the potential clinical consequences of patient non-adherence and their impact on the results of clinical trials. It was driven by a biomedical (pharmacometric) perspective that was concerned with pragmatic methods to answer empirical questions about ambulatory patients' deviations from prescribed medication, and focused on the quantitative evaluation of the degree of correspondence between the prescription and the ensuing implementation of the prescribed dosing regimen[65]. The term 'Patient Compliance' was introduced in 1975 as an official Medical Subject Heading (MeSH) in the US National Library of Medicine[66;67]. The term "pharmionics", introduced in 1987, is defined as the discipline that studies how ambulatory patients use and misuse prescription drugs[68-70].

During early research, the role of patients' views on these matters was neglected, but a later body of research addressed how prescriptions are generated, the patient's perspective in treatment choices,

and treatment management in daily life[71]. In the meantime, 'compliance' has been increasingly replaced by 'adherence'[3;72;73], as the latter term has been thought to evoke more the idea of cooperation between prescriber and patient, and less the connotation of the patient's passive obedience to the physician's instructions[74-78]. The shift from 'compliance' to 'adherence' reflects a fundamental change in understanding relationships between patients and practitioners[79-81].

It was in the light of this shift that the term 'concordance' was proposed[82;83]. 'Concordance' was first introduced by a joint working group assembled by the Royal Pharmaceutical Society of Great Britain in 1995. The 'concordance' construct recognized the need for patients and health-care providers to cooperate in the definition of a mutually agreed treatment program, acknowledging that patients and providers may have differing views[83-91].

In 1997 the American Heart Association issued a statement[92] in which adherence was defined as a behavioural process, strongly influenced by the *environment* in which the patient lives, including health-care practices and systems[93;94]. This statement contained the assumption that satisfactory adherence depends on patients' having the knowledge, motivation, skills, and resources required to follow the recommendations of a health-care professional.

In 2005, an important step was the recognition of both the intentional and unintentional aspects of non-adherence to medications[95-99]. Both facets need to be addressed simultaneously to solve this important health-care problem. The term 'medication adherence' was introduced as a MeSH term in 2009.

"Compliance" and "adherence" share the property of being quantifiable parameters, which detail when doses are taken and how much drug each dose provides. "Concordance", "cooperation", "agreement", and "therapeutic alliance" imply a certain "meeting of the minds/perspectives" of carers/caregivers and patients[100-105] regarding a treatment plan suitable for a course of pharmacotherapy, during which the patients and/or carers/caregivers bear the responsibility for correct administration of the medicine(s)[106-108]. The definition of "correct" is ambiguous in the reviewed papers, because there are certain scientific aspects of when and how much of certain drugs should be taken that are not negotiable if the prescribed medicine is to work satisfactorily, e.g. the low-dose combined oral contraceptives, the effectiveness and safety of which depend on specific doses and strict punctuality in the taking of successive doses.

Cited references

The most commonly cited text for the definition of patient compliance is a 1976 paper by Sackett and Haynes[64]. As illustrated in Table 2.1, several attempts have been taken to adapt the original definition of patient compliance in order to emphasize its psychological, behavioural, and ecological aspects. For example, the WHO definition of adherence addresses the need for patients to be involved in treatment decisions. However, this change illustrates the potential confusion triggered by a conceptual change – i.e. the implied need for prior agreement between prescriber and patient regarding the treatment plan – without regard to the measurement problem it generates. That problem arises because of the need for (a) a method to measure the coincidence of the patient's behaviour and the provider's recommendation, (b) a method for measuring agreement between the patient and care-provider, plus (c) means to avoid the resulting methodological impasse by finding ways to integrate these two dimensionally different measurements.

Table 2.1. Illustration of changes and adaptations of the original definition of patient compliance over the years

Definition	**Authors - Year**
Compliance is the extent to which the patient's behavior [in terms of taking medications, following diets or executing other lifestyle changes) coincides with the clinical prescription.	Sackett DL, Haynes BR; 1976[64]
Compliance is the extent to which the patient's behavior coincides with the clinical prescription, regardless of how the latter was generated.	Sackett DL, Haynes BR; 1976[64]
Compliance is the extent to which a person's behaviour [in terms of taking medication: following diets, or executing other lifestyle changes) coincides with medical or health advice.	Haynes R.B., Taylor D.W. and Sackett D.L.; 1979[109]
Compliance is the extent to which an individual chooses behaviours that coincide with a clinical prescription, the regimen must be consensual, that is, achieved through negotiations between the health professional and the patient.	Dracup K.A., Meleis, A.I.; 1982[110]
Adherence is the degree to which a patient follows the instructions, proscriptions, and prescriptions of his or her doctor.	Meichenbaum, D., Turk D.C.; 1987[111]
Adherence is the extent to which a person's behavior - taking medication, following a diet, and/or executing lifestyle changes - corresponds with agreed recommendations from a health care provider.	World Health Organization; 2003[3]
Adherence is the extent to which a patient participates in a treatment regimen after he or she agrees to that regimen.	Balkrishnan R.; 2005[112]

In summary, 'patient compliance' and 'medication adherence' have been the most widely-used terms, each serving as indexing terms in the Index Medicus of the US National Library of Medicine. However,

the definitions of these terms are unsatisfactory[113;114], as they are used interchangeably but inconsistently to define variation or uncertainties in the linkages between seeking medical attention, acquiring prescriptions[115], and deviating from the administration of medicines as prescribed[116-118]. Because of the breadth of the topic and the multiple behaviours that are subsumed under it, no single term (e.g. “adherence”) or definition meets all needs of the field[119-132]. There is thus a clear need to create an agreed set of rules[133], within which future activities can fit, to provide concise and adequate definitions and an associated conceptual framework that could serve the needs of both clinical research and medical practice[133;134].

2.5.2 Results from the European Consensus Meeting

At the 13th annual ESPACOMP meeting in September 2009 at Bangor University, Wales, UK, the ABC consortium coordinated the ‘European consensus meeting on the taxonomy and terminology of patient compliance’. A proposal for a sound taxonomy/terminology in the field of patient adherence was introduced by Dr. Bernard Vrijens (ABC work-package leader) who presented the research work that had been performed within the ABC project and proposed a new taxonomy.

The meeting was attended by 80 participants from Australia, Belgium, Denmark, France, Germany, Italy, the Netherlands, Norway, Poland, Portugal, Switzerland, the United Kingdom, and the United States.

Dr. Jeffrey Aronson (University of Oxford, UK) chaired the session and supervised the interactive discussion with the participants. Dr. Lars Osterberg (Stanford University School of Medicine, Stanford, California, USA) and Dr. Robert Vander Stichele (University of Ghent, Belgium) participated in a panel discussion. Discussions were recorded. During the meeting, 40 attendees participated in the electronic voting on a consensus on taxonomy in the field of deviations from prescribed treatment.

46 % of the audience indicated that they had been involved in matters relating to adherence for 2-5 years, 57 % were researchers and 25% were healthcare professionals. 48% were from academia, 15% from the pharmaceutical companies, and 8% from health services. 25% were clinically qualified as medical doctors, 30% as pharmacists, and 5% as nurses.

Most (60%) of the participants declared that the term ‘Medication Adherence’ is their preferred term for describing patients’ medicines-taking behaviour versus 25% who voted for the term ‘Patient Compliance’. When asked for the designation of a certain level of compliance (‘What does it mean to you to read that a clinical study reported a compliance level of 90%?’), the opinions were inconsistent. This finding suggests that some of the widely-used terms have quite different meanings to researchers working within different scientific and medical fields. These differences are one of the reasons why it is important to forge a uniform taxonomy that supports quantitative, pharmacometrically sound assessment. However 95 % of the audience did distinguish between how long a treatment is pursued from how well a dosing regimen is implemented. 53% of the participants considered that the terms

adherence and compliance might be used interchangeably but considered that the term 'concordance' has a distinctly different meaning than either 'adherence' or 'compliance'. A majority (61%) of the voters preferred the term 'discontinuation' to describe patients' premature ending of prescribed therapy while 37% preferred the term 'non-persistence'. Participants were then asked whether they agreed with the proposed taxonomy previously presented by Dr. Bernard Vrijens. 77% agreed with the proposed taxonomy and 72% also agreed with the proposed terminology; 15% were not sure about the proposal. If a European consensus on terminology were to be produced, 49% of the participants said that they would use it irrespective of whether they agreed with the content. 46% said that they would use it sometimes.

To broaden this discussion to a larger public it was decided to use a wiki-type collaborative web-platform. An announcement of this website has been sent to the members of the ESPACOMP mailing list (n=1321) to invite them to sign-up on this platform and to share some of their thoughts and opinions on this important topic with the wider public who are interested in patient adherence. The revised taxonomy originally posted on the wiki web-platform was well attended with up to 125 visits/day but few comments were posted.

2.5.3 A proposed taxonomy/ terminology

The new conceptual foundation for a transparent taxonomy relies on three elements, which make a clear distinction between processes that describe actions through established routines ("Adherence to medications", "Management of adherence") and the disciplines which study those processes ("Adherence-related sciences"). The proposed taxonomy is described below and the corresponding terms and definitions are summarized in Table 2.2.

Table 2.2. Summary of the taxonomy and definitions

Taxonomy	Definition
Adherence to medications	The process by which patients take their medications as prescribed, composed of *initiation, implementation,* and *discontinuation*. *Initiation* occurs when the patient takes the first dose of a prescribed medication. *Discontinuation* occurs when the patient stops taking the prescribed medication, for whatever reason(s). *Implementation* is the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose. *Persistence* is the length of time between initiation and the last dose, which immediately precedes discontinuation.
Management of adherence	The process of monitoring and supporting patients' adherence to medications by health-care systems, providers, patients, and their social networks.
Adherence-related sciences	The disciplines that seek understanding of the causes or consequences of differences between prescribed (i.e. intended) and actual exposures to medicines.

Adherence to medications

The first element is named *ADHERENCE TO MEDICATIONS,* the process by which patients take their medications as prescribed. Adherence has three components: *initiation, implementation,* and *discontinuation* (see Figure 2.4).

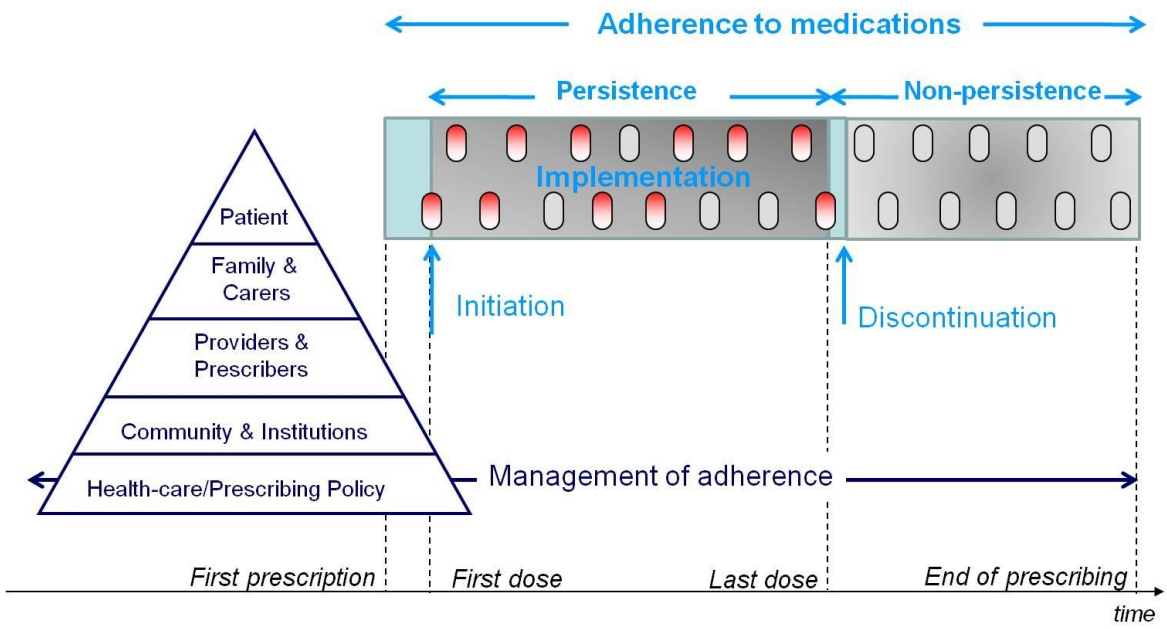

Figure 2.4

Illustration of the process of *adherence to medication* (light blue) and the process of *management of adherence* (dark blue)

The process starts with *initiation* of the treatment, when the patient takes the first dose of a prescribed medication. The process continues with the *implementation* of the dosing regimen, defined as the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from *initiation* until the last dose is taken. *Discontinuation* marks the end of therapy, when the next dose to be taken is omitted and no more doses are taken thereafter. *Persistence* is the length of time between initiation and the last dose, which immediately precedes discontinuation.

Non-adherence to medications can thus occur in the following situations or combinations thereof: late- or non-initiation of the prescribed treatment, sub-optimal implementation of the dosing regimen, or early discontinuation of the treatment.

Management of adherence

The second element of the taxonomy is named *MANAGEMENT OF ADHERENCE,* and is the process of monitoring and supporting patients' adherence to medications by health-care systems, providers, patients, and their social networks. The objective of management of adherence is to achieve the best use by patients, of appropriately prescribed medicines, in order to maximize the potential for benefit and minimize the risk of harm.

Note that the Index Medicus includes the indexing term 'medication adherence', using 'medication' as a noun modifier. We prefer the term 'adherence to medication', but the two terms can be used interchangeably. Following the same argument, "Adherence Management" can be used as an alternative to "Management of Adherence".

Adherence-related sciences

The third element is named *ADHERENCE-RELATED SCIENCES.* This element includes the disciplines that seek understanding of the causes or consequences of differences between the prescribed (i.e. intended) and actual exposures to medicines. The complexity of this field, as well as its richness, results from the fact that it operates across the boundaries between many disciplines, including, but not limited to: medicine, pharmacy, nursing, behavioural science, sociology, pharmacometrics, biostatistics, and health economics.

2.5.4 Quantification of adherence to medications

An apt quantification of adherence to medications constitutes the basis for adherence-related sciences[135]. In turn, this quantification informs the process of managing adherence, the aim of which is to help patients to take appropriately prescribed drug dosing regimens. These regimens depend on scientifically sound regulatory labelling decisions, tempered by informed practices of prescribers, and guided by evolving principles of individualized prescribing as well as the support of patients in the daily management of their medication regimens. The ultimate goal is optimal pharmacotherapy and its implicit association with optimal clinical outcomes.

Pharmionics is an adherence-related science concerned with the quantitative assessment of the three measurable components of *adherence to medications* (*initiation, implementation,* and *discontinuation*), and their respective contributions toward the effects of medicines. *Pharmionics* is thus an adherence-related science that constitutes the link to the biomedical field of pharmacometrics as a natural input to pharmacokinetic and pharmacodynamic models for quantitative analysis and projection of the consequences of correct versus incorrect dosing, and the effects of specific errors[70].

Initiation and *discontinuation* of treatment are inherently discontinuous actions, whereas *implementation* of the dosing regimen is continuous. This difference precludes a single, quantitatively useful parameter to cover all three. For example, the three patients illustrated in Figure 2.5 all took 75% of their prescribed twice-daily doses over a period of 3 months. However, the electronically compiled drug dosing history data reveal major differences in the dynamics of the three components of adherence to medications over time, which can reveal different causes and/or consequences.

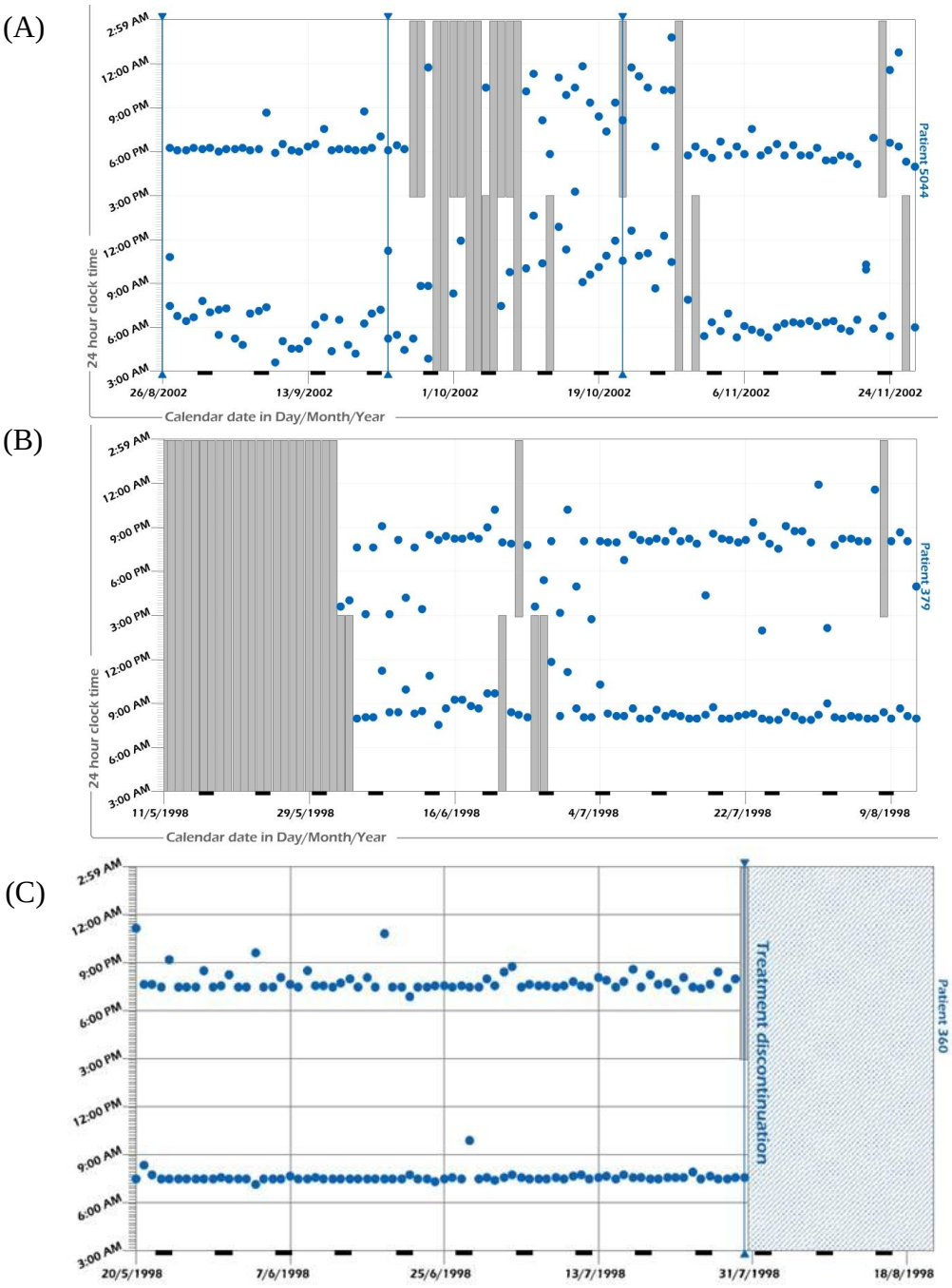

Figure 2.5

Examples of electronically compiled drug dosing history data in three patients for whom a twice daily dosing regimen was prescribed. Blue dots indicate the dates and times of drug intake. Grey bars indicate missed doses.

(A) Patient with late initiation but good implementation; (B) Patient with suboptimal implementation (missed single & consecutive doses, large variability in timing of drug intakes); (C) Patient with excellent implementation but short persistence (early discontinuation)

Initiation is often reported as the time from prescription until first dose is taken. It is thus a time-to-event variable with a well-defined time origin (prescription) and an end-point which is the first dose

taken. We note that the end-point will not be observed for those patients who never take the first dose within the studied period; in that case the end-point is censored.

Persistence, is the time from initiation until discontinuation. It is also a time-to-event variable with a well defined time origin (initiation) and an end-point which is the time of treatment discontinuation. The end-point will be censored if the end-point is not observed during the studied period.

Both variables are thus time-to-event data and should be analyzed and interpreted using standard survival analysis. Kaplan-Meier curves, median persistence, or proportion of persistent patients at a well defined time point as the most frequent representations used. We note that in clinical studies, patients sign an informed consent document, and typically the first dose is administered on site. Therefore, it is often assumed that initiation is implicit for all included patients. In that case, persistence is defined as the time from inclusion until discontinuation.

The quantification of *implementation* requires the comparison of two time-series: the prescribed drug dosing regimen and the patient's drug dosing history. Its estimation can range from a single summary statistic to a more longitudinal comparison.

The most frequent summary statistics for quantifying, within a patient, the implementation of a dosing regimen, over a defined interval of time, are:

- the proportion of prescribed drug taken;
- the proportion of days with the correct number of doses taken;
- the proportion of doses taken on time, in relation to a prescription-defined time-interval between successive doses;
- the distribution of inter-dose intervals;
- the number of drug holidays;
- the longest interval between two doses.

However, summary statistics that are estimated over an aggregate period of time have limitations, especially when one wants to depict trends in the implementation of the dosing regimen over time. It is also important to note that some sparse measures of adherence which provide only aggregate estimate over a defined period of time (e.g. counting returned tablets) do not allow one to identify precisely the discontinuation time. Thus, summary statistics based on sparse measurement methods often mix the different elements of adherence to medications and can be very confusing.

More longitudinal comparisons which make clear distinctions between initiation, implementation, and discontinuation, have been proposed, as illustrated previously using a large database of electronically compiled drug dosing histories among patients with hypertension[136].

Operational definitions for the implementation of a dosing regimen should be drug- and disease-specific. Clinically relevant definitions need to be developed, indicating which deviation from the

prescribed medication regimen is sufficient to influence adversely the regimen's intended effect[137-139]. Further discussions on operational definitions are beyond our scope and have to do with the intricacies of time series analyses. However, the proposed taxonomy forms the cornerstone for concise adherence measurement, and facilitates a smooth transition from conceptual to operational definitions.

2.6 Discussion

Despite four decades of adherence research, there is still no uniformity in the terminology used to describe deviation from prescribed regimens. Through its historical development, this field of research has operated across areas bounded by biomedical, ecological, and behavioral perspectives, the respective concepts of which are categorically dissimilar[140]. This dissimilarity has resulted in the generation of a number of concepts and terms embedded in these different disciplines, making the logical or conceptual relations between them problematic[141]. The conceptual definitions for terms vary, and partly overlap, resulting in conceptual confusion, which adds to methodological weakness in the field. This problem is further compounded by a lack of congruence between conceptual definitions, operational definitions, and measurements[20;142-146].

Because of the breadth of the topic, the multiplicity of behaviours it subsumes and their various physical dimensions, one cannot use a single term and definition to meet all needs of the field. There is, however, a clear need to create a set of rules, agreed-upon, within which future activities should fit, if all are committed to fulfilment of the need for clear, concise, and adequate definitions and an associated conceptual framework, within which work can continue. New methods and new research findings may later force a fine-tuning or even a reshaping of the field's taxonomy. Careful attention to the metrics for, and physical dimensions of, proposed terms or parameters is one of the pillars on which a sound taxonomy should rest.

Previous initiatives to standardize the taxonomy of adherence to medications were identified through the literature review. The most recent one is the attempt by the International Society for Pharmacoeconomics and Outcomes Research, but their definitions were driven by a measurement method led by refill data, which delivers only a sparse view of adherence. Our approach has integrated findings from different initiatives while remaining independent of any measurement method.

In the literature review, we have identified more than 10 different terms closely linked to the topic at hand. The proposed taxonomy is not intended to replace all of those terms. But each should find a place in the new taxonomic approach. For example, 'concordance' and 'therapeutic alliance' are elements of the management of adherence process while 'pharmionics' is an adherence related science. The main remaining controversy is between the first term introduced, "patient compliance" and the increasingly used one "medication adherence". In our view, patient compliance is synonymous with medication adherence. However, given the widely perceived, negative connotation of '(non-) compliance', and its multiple uses (e.g., compliance with drug regulations, compliance with good

clinical practice, compliance with good manufacturing practice, etc.) in many different medical and peri-medical contexts, its use should fade out over time.

2.6.1 Main findings and conclusions

More than ten different terms describing medication-taking behaviour were identified through the literature review, often with differing conceptual meanings. In response to the proliferation of ambiguous or unquantifiable terms in the literature on medication adherence, this research has resulted in a new conceptual foundation for a transparent taxonomy. The terms and definitions are focused on promoting consistency and quantification in terminology and methods to aid in the conduct, analysis, and interpretation of scientific studies of medication adherence.

2.6.2 Strengths and limitations

The major strength of this research is a sound taxonomy which has integrated findings from different initiatives while remaining independent of any measurement method.

The main limitation of this work is associated with the development of the taxonomy based on English-language literature only. This problem has been identified very early on in the process towards a unified taxonomy. During the European consensus meetings, issues regarding translation into German, French, Polish, and Dutch have been discussed. Translation remains however an important step for medical practice and teaching in the different countries. It is however important to have a set-up a sound taxonomy in the English language and translation will be the topic of further work in this field.

2.6.3 Implications and recommendations

The new taxonomy should provide researchers and clinicians with a common language for describing different experimental investigations. We hope that the proffered taxonomy will stimulate discussion, informed by shared concepts, methods, and research findings. The terms and definitions are focused on promoting consistency in taxonomy and methods, to aid in the conduct, analysis, and interpretation of scientific studies of adherence to medications. The adoption of these terms and definitions will also help to standardize the medical literature and therefore facilitate health policy decisions based on consistent evidence.

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3 Report on the Determinants of Patient Non-Adherence with Short-Term Therapies and Treatments for Chronic Diseases in Europe

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3.1 Summary

The systematic review of the literature identified 51 reviews, which recognize 771 individual determinants of patient non-adherence. The lack of standardized definitions and poor measurement methods result in many inconsistencies, which make it difficult to draw firm conclusions. Non-adherent behaviour can take many different forms and can result from many different factors, across all the dimensions identified by the WHO. Furthermore many of these factors are not modifiable. Nevertheless, patients' attitudes and beliefs appear to be the factors most closely associated with non-adherence. These factors can, however, change with time and can appear at times either to be a cause, or a consequence, of patient non-adherence. Therefore the prediction of non-adherence of individual patients is difficult if not impossible. With suitable measurement, however, non-adherent dosing patterns can come promptly into view, thus bypassing the problem of non-predictability.

Self-reported non-adherence among 2630 patients from 11 different EU countries to antihypertensive medicines is prevalent. 42% of the participants reported to be non adherent; 18% of which is claimed to be intentional. Prevalence differs substantially across the sampled European countries. While a proportion of this variance is explained by country-level effects, the principal finding of this study is that low perceived self-efficacy and, to some extent, high perceived barriers and cost-related behaviour (strategies to cope with the cost of prescriptions), are consistently associated with non-adherence across Europe.

A discrete choice experiment was used to examine patients' stated preference for persistence with medications. The results of the study suggest that in addition to treatment benefits, patients place a high value on two factors: (a) the reduction of risk of severe (but rare) ADRs and (b) the frequency of dosing, when choosing whether to continue or not with the taking of a particular medicine. Persistence is therefore associated with a willingness to trade between potential benefits, harms, and inconvenience. We note that this finding mirrors the determination by pharmaceutical experts of the optimal dose and dosing regimen during the drug development process, in order to achieve the best balance of benefits, risks, and convenience of dosing. Different combinations of these attributes may have value in assessing patients' likelihood of persisting with medicines, and may provide useful support for the personalization of pharmaceuticals and treatment regimens to maximize persistence.

Finally, through the survey conducted about the adherence to short-term antibiotic treatment, in the same sample of patients, self-reported non-adherence was about half that to chronic-use, anti-hypertensive medications. Reasons for not initiating or not completing antibiotic treatment are closely associated with clinical effects (adverse effects or/and perceived efficacy). Acknowledged reasons for poor implementation of the dosing regimen appeared mainly to arise from forgetfulness. Adherence to long-term treatment of chronic diseases and to short term treatment of acutely symptomatic conditions is very different. Here again, reliable and detailed measurement of patients' dosing histories remains the cornerstone of realistic, practical approaches to identify and characterize patient non-adherence.

3.2 Introduction

The development of interventions to enhance patient adherence and maintain long term persistence, requires an understanding of the determinants of patient non-adherence to prescribed therapies. This is especially important when the determinants are modifiable risk factors, which, once identified, can then be targeted for beneficial changes.

Published literature identifies hundreds of determinants of non-adherence but without consistent findings that would indicate their relative importance on the 3 identified components of patient adherence: initiation, implementation, discontinuation. For example, the WHO recommends classification of determinants in 5 dimensions but provides little or no closure in respect to outcomes:

- Socio-economic factors
- Healthcare team and system-related factors
- Condition-related factors
- Therapy-related factors
- Patient-related factors

Finally, little information exists on short-term adherence for acute diseases versus long-term adherence for chronic diseases.

In this work package, we have addressed the identification of determinants of adherence in 2 steps:

- A retrospective systematic review of the literature, wherein we have adopted the method of reviewing reviews
- A prospective survey across EU countries
  - To identify the determinants of patient non-adherence to one particular class of chronic-use medications: anti-hypertensives
  - To examine patients' stated preference for persistence with medications through a discrete choice experiment.
  - To investigate determinants of patient non-adherence to short term antibiotic treatment, with a comparison to the chronic use of anti-hypertensives in the same sample.

3.3 Objectives

- To perform a systematic review to identify the determinants of patient adherence with short-term and long-term therapies in Europe
- To analyse the factors responsible for non-adherence to treatments for acute diseases, and chronic conditions for different clinical sectors, health care settings and population segments

- To identify the factors which influence patients' decisions in relation to the process of execution of short-term treatment and continuation with long-term treatments
- To quantify patients' preferences for a range of attributes relating to the decision-making process of being adherent or non-adherent

3.4 Determinants of patient adherence: a review of systematic reviews

Przemyslaw Kardas, Pawel Lewek, Michal Matyjaszczyk

3.4.1 Summary

Background: A number of potential determinants of patient non-adherence to medication has been described so far in the medical literature. However, heterogenic quality of existing publications on non-adherence poses the need for use of rigorous methodology in building a list of such determinants. We decided to create such a list on the grounds of recently agreed European consensus taxonomy and terminology of patient adherence.

Objective: The objective of this research was to design a comprehensive, yet evidence-based list of determinants of patient adherence, according to a systematic review of current literature.

Methods: MEDLINE, EMBASE, CINAHL, the Cochrane Library, (IPA), and PsycINFO were systematically searched for systematic reviews that provided determinants on patient non-adherence to medication. The searches were limited to papers in the English language published between 2000/01/01 and 2009/12/31, having adherence to medication supposed to be taken in the outpatient settings prescribed by health professionals as a major topic of publication. Studies that primarily focused on adherence-enhancing interventions were excluded from this review.

Results: Fifty-one systematic reviews were included in this review, covering 19 different disease categories. Identified studies exclusively assessed non-adherence to chronic therapies. In these studies, 771 individual factor items were identified, out of which most were determinants of implementation, and only 47 were found to be determinants of persistence with medication. Factors with unambiguous effect on adherence were grouped to finally form 419 individual determinants (among these, 162 with positive, 155 with negative, and 102 with neutral effect on adherence), which were further grouped in 8 clusters of socio-economic-related factors, 6 clusters of healthcare team- and system-related factors, 6 clusters of condition-related factors, 7 clusters of therapy-related factors, and 14 clusters of patient-related factors.

Conclusions: Our analysis provides clear evidence that medication non-adherence is a summary effect of multiple determinants, belonging to several different fields. Consequently, multifaceted interventions may be the most effective answer toward unsatisfactory adherence, and its consequences. Limited number of publications assessing determinants of persistence with medication, and lack of those providing determinants of adherence to short-term treatment identify areas worth covering with future research.

3.4.2 Introduction

Enormous progress in the field of both medicine, and pharmacy, that took place in the last century, led to the completely new paradigm of treatment. Contrary to the past, in which effective treatments were only available in hospital settings, effective remedies are available now in ambulatory settings. At the same time, demographic changes that happen to both developed, and developing countries, make chronic conditions still more prevalent. All this makes most modern treatments dependent on patient self-management. Surprisingly often, evidence based treatments fail to succeed because of a human factor – known for few decades as *patient non-adherence*.

Growing literature on patient non-adherence described numerous determinants of this patients' behaviour. In one of the often-cited reports, the number of these determinants is estimated at the level of over 200[16]. Unfortunately, serious drawbacks of methodology of numerous studies make revising this list a needed. Only recently a new rigorous taxonomy and terminology of adherence was agreed on thanks to European consensus that creates the ground for objective comparisons of adherence-related study results[1].

Therefore, in order to design a comprehensive, yet evidence-based list of determinants of patient adherence, for both practical use in clinical settings, and theoretical one to inform adherence-enhancing interventions, we have performed a systematic review of current literature.

3.4.3 Objectives

The objective of this research was to identify and classify the determinants of non-adherence with short-term and long-term treatment for different clinical sectors, health care settings and population segments due to the systematic search of the current literature.

3.4.4 Methods

3.4.4.1.Eligibility criteria

According to very high number of publications with keyword 'patient compliance', and 'patient compliance' as major MESH term (close to 50.000 hits, and 16.000 in PubMed database by 2009/12/31, respectively), we decided to include recent systematic reviews in this search only. Thus, we included systematic reviews in the English language, published between 2000/01/01 and 2009/12/31, having adherence to medication supposed to be taken in the outpatient settings prescribed by health professionals, as a major topic of publication, if they provided determinants of adherence.

3.4.4.2 Exclusion criteria

Papers were excluded for the following reasons:

1. Studies that primarily focused on adherence-enhancing interventions. 2. Studies that were not systematic reviews. 3. Studies that assessed adherence to non-medication intervention (e.g. vaccination) 4. Double citations 5. Determinants of adherence to medication not provided. No paper was excluded on the grounds of quality.

3.4.4.3 Information sources

MEDLINE (through PubMed), EMBASE, CINAHL, the Cochrane Library, International Pharmaceutical Abstracts (IPA), and PsycINFO were searched for all systematic reviews providing determinants of patient adherence. The searches were limited to papers in the English language being published between 2000/01/01 and 2009/12/31. Search strategy was designed to include all relevant publications, that is why a number of possible synonyms for *medication adherence* (i.e. *patient compliance, concordance, patient dropouts, treatment refusal,* and *directly observed therapy*), in combination with several synonyms of *determinants* were accepted. Detailed search strategy for MEDLINE database (through PubMed) is provided in Appendix 3.1. For the other databases, the search strategies were adopted accordingly.

3.4.4.4 Study selection

Eligibility assessment of title and abstract was performed independently in an unblended standardized manner by two reviewers (PK, PL). If at least one reviewer coded a study as potentially eligible, the paper was included for full-text review. The full texts of potentially eligible papers were retrieved and reviewed in the second stage of the screening process. Disagreements were resolved by discussion and a final decision was reached between the two reviewers.

3.4.4.5 Data collection process

A structured data collection sheet was developed to extract data from each study. All available relevant data were extracted from the papers; no additional information was sought from authors. The following paragraphs describe which data were extracted.

3.4.4.6 Data items

Determinants of adherence to medication

A range of determinants were extracted, according to reporting in the source publications. These were further categorized according to their effect on adherence to medication, using the model of matrix of adherence determinants (Figure 3.1). Relevant dimensions included:

- *Treatment duration*: *long-* versus *short-term* treatment;
- *Components of adherence to medication*: *implementation* of the dosing regimen (defined as the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen) versus *persistence* (defined as the length of time between initiation and the last dose which immediately

precedes discontinuation)[1]. Determinants were categorized under implementation unless original study wording clearly addressed persistence.

- *Direction of effect*: determinants were classified according to their *positive, negative, neutral,* or *not defined* effect on adherence;
- *Dimensions of adherence*: these were *socio-economic factors, healthcare team- and system-related factors, condition-related factors, therapy-related factors, and patient-related factors.* In this was original WHO report description followed[2], with a modification: demographic variables were included under patient-related, instead of socio-economic related factors.

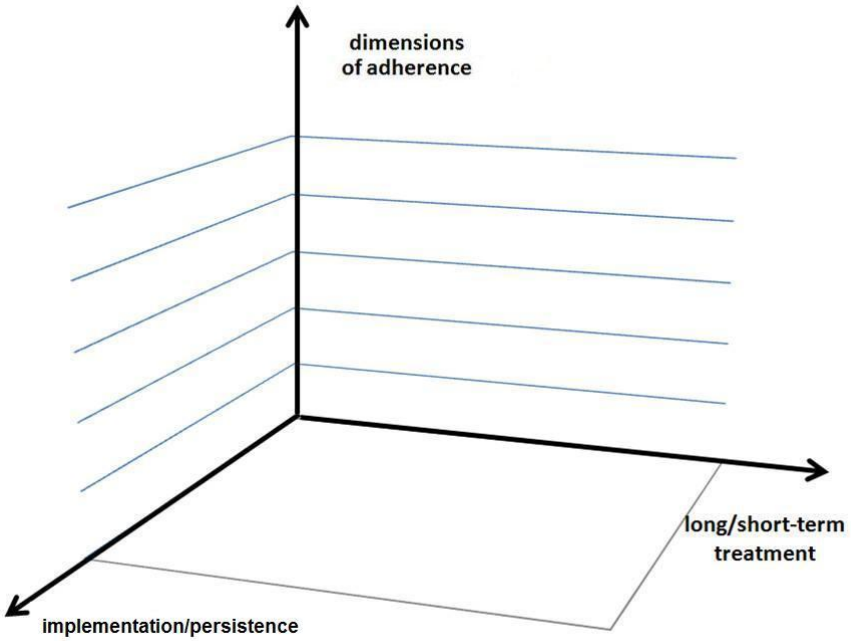

Figure 3.1

Model of matrix of adherence determinants for categorization of adherence determinants identified in the literature search.

Forth axis (direction of effect: positive vs negative) not shown. Dimensions of adherence included socio-economic factors, healthcare team and system-related factors, condition-related factors, therapy-related factors, and patient-related factors.

Other data

Other data extracted from the studies included scope of the review (medical condition, class of drugs, etc.), studied population, and databases searched by the authors.

3.4.5 Results

3.4.5.1 Study selection

Fifty one systematic reviews were included in this review. An overview of the review process and reasons for exclusion at the different steps are detailed in Figure 3.2.

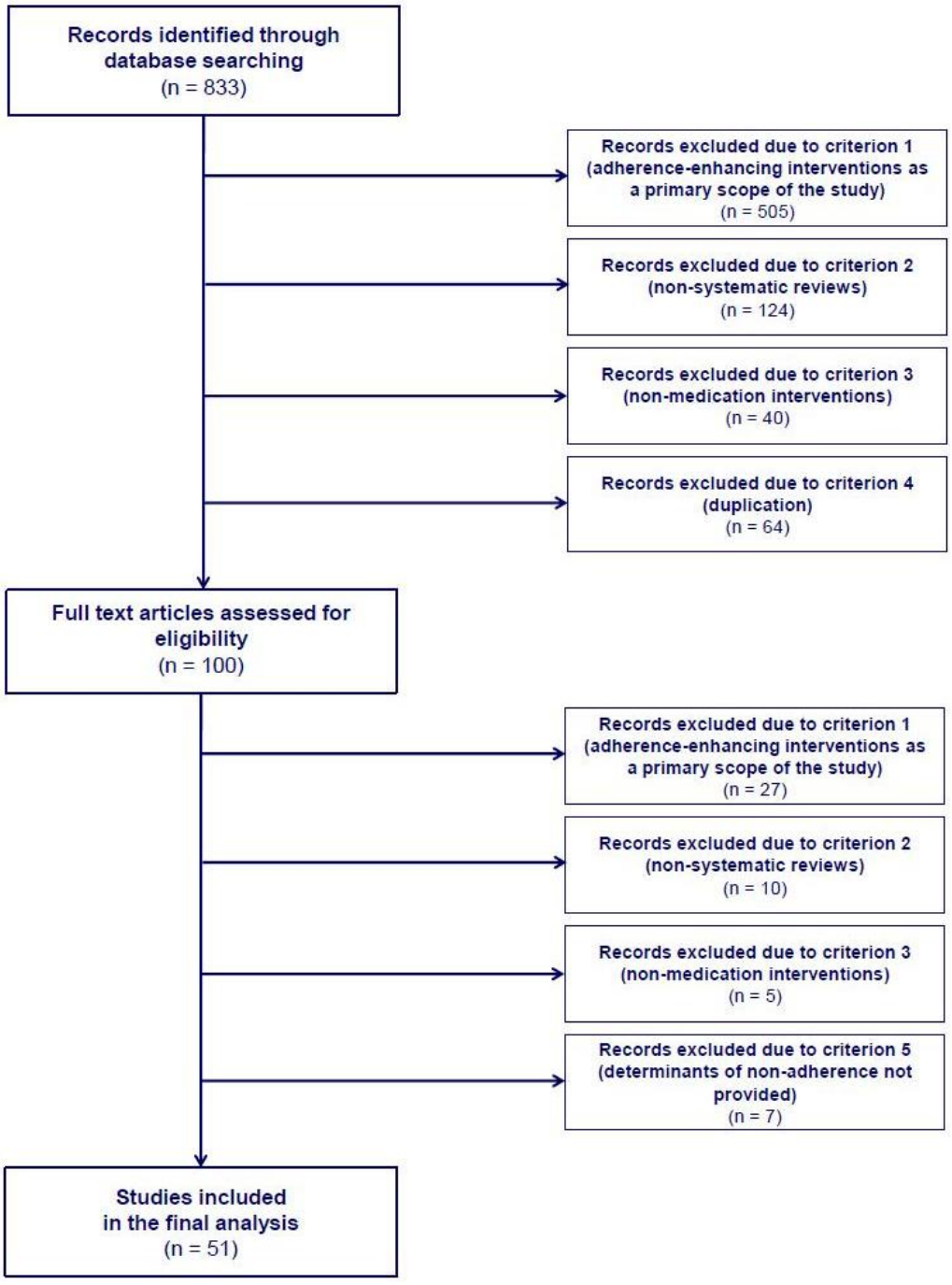

Figure 3.2

Flow diagram of study selection process.

3.4.5.2 Study characteristics

Individual study characteristics are listed in Appendix 3.2. The majority of the studies were systematic reviews. However, 8 of the studies[3, 13, 14, 15, 16, 19, 22, 41] were also enriched with meta-analyses of relevant data.

Within our selected reviews, the most common field of the studies was general population (9 reviews) [8, 9, 10, 13, 14, 15, 16, 28, 48, 49], followed by HIV (8 reviews) [17, 33, 34, 35, 41, 42, 43, 50], and psychiatric conditions (8 reviews)[7, 25, 29, 30, 37, 38, 40, 45] (Table 3.1). Disease categories were broad (19 different diseases); studies exclusively reported patients with chronic diseases.

Close to half of studies (25 out of 51) did not specify the age group of patients covered by the review. Out of the rest, those dealing with adults were the most prevalent ones (11 studies, Table 3.2).

Table 3.1. Fields covered by the selected studies.

Field	No of studies
General population	10
HIV	8
Psychiatric conditions	8
Diabetes	3
Hypertension	3
Cancer	2
End stage renal disease	2
Multiple sclerosis	2
Osteoporosis	2
Transplantations	2
Tuberculosis	2
Cystic fibrosis	1
Skin diseases	1
Glaucoma	1
Heart failure	1
Malaria	1
Opioid dependence	1
Non-malignant chronic pain	1

Table 3.2. Patient groups covered by the selected studies.

Patient group	No
not specified	25
Adults	11
Children + Adults	8
Children	4
Elderly	2
Youth	1

3.4.5.3 Determinants of adherence to medication

As many as 771 individual factor items were extracted from reviewed literature. All these were corresponding to determinants of long-term treatment; no determinants for short-term treatment were found. Vast majority of individual factor items were determinants of implementation, and only 47 were found to be determinants of persistence with medication.

For 64 individual factor items, no unambiguous information on their effect on adherence to medication could be found in the source publication. All the other factors were grouped to finally form 419 individual determinants (among these, 162 with positive, 155 with negative, and 102 with neutral effect on adherence). These were further clustered according to dimension of adherence (Tables 3.3-3.7), thus standing for socio-economic-related factors (8 clusters), healthcare team- and system-related factors (6 clusters), condition-related factors (6 clusters), therapy-related factors (7 clusters), and patient-related factors (14 clusters), respectively.

Table 3.3. Socio-economic factors affecting adherence.

Factors having		
negative effect on adherence	**positive effect on adherence**	**neutral effect on adherence**
Family support		
• lack of family support [11, 37] • irregular supervision by a family member [36P] • child selfresponsibility for taking medication [26]	• family support [11, 36, 37] • family financial support [30, 36] • family support in executing medication [38, 30, 36]	• family emotional support [30, 51] • family involvement during hospitalization or follow-up [29]
Family/caregivers factors		
• disorganized biologic families [26, 27, 50] • family in conflict [15, 38, 50, 51] • responsibilities in the home (such as providing income and caring for children) [36] • low parental educational level [50] • family beliefs about the nature of the patient's illness [25] • more people in household (in children) [15] • having several adults involved in pill supervision [50]	• two-parent families [7P] • family cohesiveness [15] • having an adult other than the biologic parent as primary caregiver [43] • higher caregiver education level [43] • responsibilities in the family [36] • parental belief that ADHD is a biological condition [7P] • mother's perception of the severity of	• knowledge of family members regarding disease [29] • family member with mental illness [30] • number of people in the household [48] • parental marital status [7P]

	disease [21]	
Social support		
• lack of social support [11, 17, 34, 35, 38, 46, 51] • less acculturation [30] • low social functioning [37] • low social rank of an illness [38] • negative publicity regarding HAART or the medical establishment [35]	• social support [15, 20, 25, 27, 35] • emotional support [15] • good social adjustment [37, 40] • including significant others into therapeutic alliance [38] • supervision of medication administration by others [25, 51] • patients' support to patients [11, 36]	• social support [43]
Social stigma of a disease		
• stigma of a disease at school, at workplace, among the family and friends [36, 50, 79] • negative attitude in the patient's social surroundings towards psychiatric treatment [38] • fear of disclosure and wanting to avoid taking medications in public places [35] • disclosure of the child's HIV status [50]	• openly disclosing HIV status to family and friends [35]	

• hiding the disease (TB) for fear that employers may discover it [36]		
Costs of drugs and/or treatment		
• cost of drugs (co-payment) [32, 46, 18P] • costs of drugs and treatment [36P, 11P]		
Prescription coverage		
• lack of, or inadequate medical/prescription coverage [7 P, 11P, 30, 46] • fear of asking for money from employer to purchase drugs (in TB) [36]	• having health insurance [30]	
Socioeconomic status		
• low income [46] • poverty [11P, 36 P, 50] • lower socioeconomic status [30] • financial constraints [35, 38] • wanting to remain sick to qualify for financial support [36]	• higher income [24, 16, 36] • higher socioeconomic status [16, 7P]	• socioeconomic status [7P, 27, 36, 44, 48, 51] • financial support from outside the family [30]
Employment status		
• unemployment [37] • white-collar employment [24]	• being employed [21]	• employment status [27]

TB – tuberculosis, P – determinant of persistence

Table 3.4. Healthcare team and system-related factors affecting adherence.

Factors having		
negative effect on adherence	**positive effect on adherence**	**neutral effect on adherence**
Barriers to healthcare		
• barriers to high-quality care [30] • lack of providers/caregiver availability [7P, 50] • rural settings [50] • poor access to a health care facility (e.g. long waiting times, queues, lack of privacy, inconvenient appointment times, inconvenient opening hours) [36] • seeing different language speaking therapist (i.e. Spanish-speaking therapist in US Latinos) [30] • difficulty in obtaining sick leave for treatment [36] • having no time to refill prescriptions, or other pharmacy-related problems [35]	• good access to medication and health service [17] • good access to a health care facility [36, 37] • non-emergency referral [40] • seeing the same language therapist (i.e. Latino therapist, in US Latinos) [30] • obtaining certification of preventive treatment (for immigrants to US) [36]	• access to care [29] • greater distance from the clinic [24, 36] • current inpatient status [29] • rural settings (vs urban) [29] • type of transportation used [29]
Drug supply		
• poor drug supply (e.g. poor TB medication availability at health care facilities) [36, 35, 35] • unavailability of medications (e.g. prescription ran out) [49]	• receiving treatment together with methadone from a street nurse (for DOT in TB, in IDU patients) [36]	
Prescription by a specialist		
	• referral/prescription by a specialist [47, 40]	• prescription by a psychiatrist (in depression) [30]

Information about drug administration		
• unclear information about proper drug administration [49] • greater number of prescribing physicians [49] • conflicting messages between GPs and specialists on medication [21] • discrepancies between treatment guidelines and common clinical practice (as patients try to ask several specialists [38] • use of multiple pharmacies [49]	• doctor's ability to provide appropriate information as to the drug administration [48, 51] • being given information about the action of the drugs [39]	
Healthcare provider-patient communication and relationship		
• poor healthcare provider-patient relationship [6, 11, 21, 29, 36, 39, 49] • poor patient–physician communication [6, 21, 25, 36, 48] • lack of trust in doctors and healthcare [6, 35] • lack of patient satisfaction with their healthcare, [21, 35] • limited caregiver adherence strategies [50]	• good and stable doctor-patient relationship, good therapeutic alliance [7P, 25, 37, 38, 48] • quality, duration and frequency of interaction between the patient and doctor [48] • offering enough time to the patient, leaving space to talk about problems concerning medication or side effects [38] • patient involvement in decision making [18P, 35, 44] • encouraging self-management [51] • doctor responsiveness [48] • doctor's ability to demonstrate empathy [48]	

	• doctor's ability to elicit and respect the patient's concerns [48] • good patient–healthcare provider communication [18P, 23, 36] • trust in the health-care provider [8, 35] • perceived healthcare provider support [11, 17]	
Follow-up		
• inadequate discharge planning [25, 29] • fewer outpatient visits [6, 25, 39] • poor follow-up by providers [29, 36]	• more outpatient visits [47, 49] • more visits to a nonmedical therapist [30] • seeing a greater number of physicians [44] • good follow-up by healthcare providers [18P, 43]	• clinic attendance [24]

GP – general practitioner, TB – tuberculosis, ^{P} – determinant of persistence

Table 3.5. Condition-related factors affecting adherence.

Factors having		
negative effect on adherence	**positive effect on adherence**	**neutral effect on adherence**
Presence of symptoms		
asymptomatic nature of the disease or absence of symptoms [11, 18P, 39, 48]	increased severity and number of symptom [5, 7P, 30, 36, 37] disability [11, 48]	• pain duration [6] • pain intensity [6] • presence of tremor [24]
Disease severity		
lower affective pain ratings [6] detectable viral load (in HIV-infected youth) [79]	disease severity [13, 79, 47, 44] perceptions of disease severity [13] more hospitalization (before starting ART in children) [50]	• disease severity [8, 12, 13, 16, 25, 30, 51] • worse clinical status [17] • possible consequences of missed doses [12]
Clinical improvement		
clinical improvement, disappearance of symptoms, feeling better / cured [36P, 38P, 44, 35, 38] onset of clinical symptoms (in latent TB infection) [20]	perception of a clinical improvement [38] reduced viral load (in HIV-infected youth) [79]	
Psychiatric condition		
psychiatric disorders [37, 48] negative symptoms/motivational deficits [38]	lower rates of narcissistic-histrionic personality disorder (in depression) [40]	• severity of psychotic symptoms [29]
Certain diagnoses/indications		

certain diagnoses (pulmonary conditions, DM, and sleep disorders vs other) [16] indication (pain medication vs other medications) [6]	certain diagnoses: rheumatoid arthritis vs other types of arthritis [6], combined subtype in ADHD, vs inattentive or hyperactive subtype [7P], disease group (HIV, arthritis, GI diseases, and cancer vs other) [16], disease group (diagnosis other than personality disorder and substance abuse, in depression) [40] estrogen receptor positive (in breast cancer) [44]	• cause of ESRD [27] • latent or active TB [36] • disease factors [48]
Duration of the disease		
chronic nature of the disease [21] longer time since clinic visit [39] longer time since transplant [23] later disease stage (in HIV-infected youth) [79] shorter duration of illness (in schizophrenia) [29]	longer duration of pain [8]	• duration of the disease [30] • length of time of hemodialysis [27, 46]

ART – antiretroviral therapy, ESRD – end stage renal disease, TB - tuberculosis, P – determinant of persistence

Table 3.6. Therapy-related factors affecting adherence.

Factors having		
negative effect on adherence	**positive effect on adherence**	**neutral effect on adherence**
Adverse effects		
• adverse effects [5P, 7P, 11, 11P, 17, 18P, 21, 25, 27, 32, 35, 36, 38, 79, 46, 46, 48, 49, 50, 51] • decreased quality of life while taking medications [21, 35]	• less adverse effects [8, 40]	• adverse effects [29, 39]
Patient friendliness of the regimen		
• complexity of the regimen (e.g. complex/frequent dosing schedule/number of tablets) [5, 17, 18P, 25, 35, 36P, 38, 46, 48, 47, 50, 51] • number of prescribed medications (polymedication) [6, 48] • less medication prescribed (in patients with chronic non-malignant pain) [6] • dosing frequency [7P, 9, 21, 35, 39, 47, 48, 50] • doses during day (particularly the middle-of-day or early-morning doses) [7P, 35] • instability of the regimen [47] • inconvenience associated with administration of some medication (e.g. oral biphosphonates) [5,	• once-daily dosing (vs more frequent one) [12, 22, 31, 41, 52] • once-weekly dosing (vs once-daily) [28] • simple regimen [35] • fewer drugs prescribed [79, 12] • fixed-dose combination pills [10, 53] • long acting formulation [7P] • unit-of-use packaging [10] • flexibility/patient choice in treatment [3P, 36] • dosing through injections [32, 38, 46, 48] • regular medication schedule (vs irregular dose interval) [47]	• simplicity of regimen [12] • regimen complexity [27, 29, 39] • number of prescribed medications [8] • once-monthly dosing (vs once-daily) [28] • route of medication administration [29] • use of oral medication (vs depot ones) [29]

18P, 21, 39] • injection formulation (e.g. insulin) [5, 11, 12, 36P] • need to adjust dietary habits for taking medication [17, 21, 35, 36, 50] • problems with opening containers [49] • disliking aspects of the medication [44] • poor taste of medication [35, 46, 51] • big tablet size, problems with swallowing tablets [35, 46, 49, 51]		
Cost of medication		
• cost of medication [21, 32, 48, 50]		
Drug effectiveness		
• drug ineffectiveness, objective or perceived [5, 7P, 11 P, 36 P, 38, 49]	• relief of symptoms [36P, 51] • objective drug effectiveness [11, 35, 53]	
Duration of the treatment		
• longer duration of treatment [36P, 79, 48, 50, 52]	• shorter duration of treatment [20]	• duration of treatment [44]
Drug type		
• drug type (olanzapine vs risperidon) [45P] • higher antipsychotic dose [29]	• drug class (aRB vs ACEi, BBs, CCBs, diuretics) [4P] • drug class (fluoxetine, nortriptiline, or imipramine, vs other antidepresants) [40], (fluoxetine vs others) [30P, 40] • boosted protease inhibitors (vs standard	• class of medication [25, 29] • dose of prednisone [24] • type of treatment program (in TB) [36]

	therapy) [42] • greater methadone doses [3P]	
Well organised treatment		
	• receiving care in structured settings (e.g. DOT) [34] • treatment at medical centre [7P] • well-structured treatment plan [38] • psychotherapy (along with psychotropic medication) [30]	• medication supervision status [29] • having a case manager [29] • being aware of monitoring [52]

ACEi – angiotensin-converting-enzyme inhibitors, aRB - angiotensin II receptor antagonists, BBs – beta-blockers, CCBs – calcium channel blockers, DOT – directly observed therapy, [P] – determinant of persistence

Table 3.7. Patient-related factors affecting adherence.

Factors having		
negative effect on adherence	**positive effect on adherence**	**neutral effect on adherence**
Age		
• younger age [25, 37, 44, 46] • older children (vs younger ones) [51] • age - older and younger age groups (vs adults) [36] • very old age (older than 85 years) [44]	• older age [8, 17, 24, 27, 30, 47, 44] • younger females (vs older ones) [38]	• age [16, 20, 21, 29, 38, 39, 43, 44, 48, 49]
Gender		
• male gender [37, 39, 46]	• female gender [8, 25, 36, 38, 40] • male gender [7P, 24]	• gender [6, 7P, 16, 17, 20, 27, 29, 30, 43, 47, 48, 49]
Marital status		
• single or divorced (vs married) [24, 25] • being married (in psychosis) [37]	• being married [15, 21, 30, 40] • living with someone (vs living alone) [15] • living alone/being single (in psychosis) [37]	• marital status [27, 29, 48, 49] • orphan status [50]
Education		
• illiteracy [36] • having repeated a grade in school (in HIV-infected youth) [79]	• education [16, 20, 25, 36, 37, 40, 46] • being in school (vs not being, in HIV-infected youth) [79] • high IQ [40]	• education [6, 27, 29, 30, 39, 47, 49]
Ethnicity		

• Latinos (vs Euro-Americans) [30] • Hispanic patients (in the US, in TB) [36] • monolingual Spanish speakers [30] • non-white women [44]	• Caucasian race [7P, 24] • U.S. born [24]	ethnicity [27, 29, 46, 20, 43, 47, 49] place of birth [20]
Housing		
• unstable housing [79] • homelessness [35] • residentially mobile [36] • being away from home [27, 35, 46, 50]	• stable housing [20, 25] • structured environment away from home [36]	homelessness [20, 36] living arrangements [29, 30, 49]
Cognitive function		
• cognitive impairment, low attention and working memory [17, 33, 37, 46]		neurocognitive impairment [29, 33] verbal fluency [33]
Forgetfulness and reminders		
• forgetting [17, 35, 46, 49, 51] • sleeping through a dose [35]	• making use of reminders [35, 36] • using friends and family as reminders [35] • having a routine in which taking drugs could be easily incorporated [35]	
Knowledge		
• lack of comprehension of disease and treatment [27, 32, 48, 50] • misunderstanding of the prescription and treatment instructions, and the consequences of	• knowledge of disease [7P, 18P, 39] • situational operational knowledge [24, 35] • understanding the need for strict adherence [35]	

non-adherence [36, 49, 50, 35] • misconceptions reported from the media, lay press, family or friends, about a medication [21] • obtaining helpful breast cancer information from books or magazines (in breast cancer) [44]		
Health beliefs		
• denial of diagnosis [36, 48] • unrealistic expectations concerning the medication's benefit/risk ratio [38] • negative patients' beliefs about the efficacy of treatment [34, 35, 36, 51] • negative attitude toward or subjective response to medication [29] • thinking that the treatment could make the patients ill [36] • belief that taking medication together with concurrent western or traditional medicines may have negative consequences (in TB) [36] • belief that pregnancy would increase intolerance to drugs and make TB drugs ineffective [36] • concerns that the treatment would affect immigration status, and lead to disclosure of illegal immigrant status/incarceration (in TB) [36]	• belief in the diagnosis [48] • belief in a particular set of health recommendations [48] • belief in self-efficacy for taking medication [8] • self-confidence to maintain health status [47] • belief in the efficacy of the treatment [35, 36, 79] • fewer concerns about drugs, belief that medication is safe [7P, 8] • belief that asthma is not caused by the external factors [8] • lower belief in natural products and home remedies [8] • beliefs of control over one's health [8] • feeling of empowerment [5] • lower control beliefs about cancer-related pain [8]	• HIV disease attitudes [17] • feeling invulnerable to the consequences of HIV [43]

• having doubts, or not being able to accept HIV status [35] • unresolved concerns about time between taking the drug and its effect [48] • being suspicious of treatment/medical establishment [35] • interpreting DOT as distrust [36] • "being tired'' of taking medications [36P] • feeling that treatment is a reminder of HIV status [35] • perceived excessive medication use [49] • feeling persecuted or poisoned [38] • lack of interest in treatment [36] • wanting to be free of medications or preferring a natural approach [35] • wanting to be in control [35] • prioritizing work over taking treatment [36]	• perceived benefits of adherence [8, 11, 20, 20, 27, 36] • desire to avoid burdening family members [11] • more motivation [30] • belief that they are vulnerable or susceptible to the disease or its consequences [48] • worrying about the disease [51] • perceived the necessity of treatment [8, 20] • regarding drugs as vital (as opposed to important) [39] • felt less burdened by taking the medication [8] • fear of experiencing relapses and future disability [11]	
Psychological profile		
• personality: low conscientiousness, high cynical hostility [27] • pessimistic ways of coping [51]	• accepting the HIV-seropositivity [35] • coping psychologically with HIV diagnosis [36] • optimistic ways of coping [51]	• coping style [27] • emotional overinvolvement [30] • warmth [30]

• withdrawal coping style, or self-destructive escape coping style [79] • poor insight [29] • lack of self-worth [35] • oppositional behaviours [51] • laziness/lack of care [36] • being too distracted or busy [35]	• hope [11] • insight [37] • higher self-efficacy [11, 24] • higher self-efficacy for adopting medication compliance behaviours [79] • higher levels of life satisfaction [79] • internal locus of control [46] • self-esteem [11, 35] • lower levels of psychologic distress [79] • personal control of the disease and therapy [51, 11] • higher level of self-care agency score [24] • living for someone, especially, children [35] • rewarding oneself after injections [11]	• more insight [30] • criticism [30] • less busy lifestyle [8] • problems with role functioning [30]
Comorbidities and patient history		
• having other concurrent illnesses affecting adherence [35] • non-adherence in the past [29, 37] • previous treatment failure [21] • concurrent diseases or illnesses, including malnutrition [35]	• less chronic co-morbidities [47] • more severe comorbid conditions [7P] • no previous use of disease modifying therapies (in MS) [11] • previous psychiatric contacts (in patients with psychosis [37]	• number of medical conditions [8] • adherence to other parts of an inpatient treatment program [29] • presence of mood symptoms (or diagnosis of schizoaffective or bipolar disorder) [29] • anxiety [13]

• psychiatric illness, e.g. anxiety/depression [21, 24, 27, 34, 35, 36, 37, 79, 46] • prior suicide attempt [79] • concomitant medication use (in latent TB) [20] • recent hospitalization [20] • long hospital stay [37] • higher number of transplants and rejection episodes [24] • both eye blindness [39] • impaired motor functioning [33] • history of infection (in patients after kidney transplantation) [24] • no history of diabetes [24] • sexual abuse under age of 12 years [79] • recent incarceration [34] • receiving standard primary tumour therapy (in tamoxifen use in breast cancer) [44P]	• previous use of antidepressants (in depression) [40] • witnessing the consequences of not following medical advice in relatives with other diseases [11] • prior history of treatment with stimulants (in ADHD) [7P] • current psychiatric treatment (in depression) [40] • being less likely to have bartered sex during the lifetime (in HIV-infected youth) [79] • being less likely to have had a sexually transmitted disease since learning their serostatus (in HIV-infected youth) [79] • using condoms with recent sex partners (in HIV-infected youth) [79] • diagnosis of asthma or COPD (in HF patients) [47] • lack of relapse (in depression) [40] • recent exposure to TB [20] • previous readmission for all causes (in HF) [47] • previous readmission for HF (in HF) [47]	• concurrent methadone treatment (in latent TB infection) [20] • total number of therapists in lifetime [30] • number of medications prescribed for another condition [39] • diabetes, as a comorbidity [27] • dialysis compliance [24] • type of the dialysis [27] • patient's transplant history [26, 27] • donor/graft source [24, 26] • treated rejection episodes [24]
Alcohol or substance abuse		

• substance abuse [29, 30, 34, 35, 36, 37, 38] • injection drugs use (vs non-injection ones) [34] • younger age of first marijuana use [79] • alcohol abuse [38] • smoking [46]	• less recent drug use in the previous 3 months (in HIV-infected youth) [79] • medication taking priority over substance use [35] • drug addiction treatment, especially substitution therapy (for HIV treatment in drug users) [34] • drinking less, or non-drinking [21, 79] • non-smoking [21]	• injective drug using [36]
Patient-related barriers to compliance		
• transportation difficulties [35, 46]		

HF – heart failure, MS – multiple sclerosis, TB - tuberculosis, ^{P} – determinant of persistence

3.4.6 Discussion

3.4.6.1 Main findings and conclusion

In this systematic literature review, we identified 51 systematic reviews on the determinants of adherence of medication. Remarkably, despite broad range of the fields covered with these publications, we have not identified any publication primarily focusing on short-term therapies, nor the individual determinants of patient adherence to short-term treatment.

Noteworthy is also the fact that a vast majority of reviewed literature provided only determinants of implementation. In fact, many studies lacked clear definition of adherence, thus living some space for interpretation in view of distinction between implementation and persistence. In this study, such cases were arbitrarily classified under determinants of implementation, assuming that in most of cases, authors were interested in day-to-day drug taking. Only recently a European consensus on taxonomy and terminology of adherence was agreed upon, making a step toward more precise reporting of research findings in the field of adherence to medication[1]. However, interpreting results of this study, one has to have in mind this limitation.

Many studies reported positive effect of family and social support on adherence, and a negative effect of the lack of such support (Table 3.3). Social stigma of a disease may also be responsible for non-adherence in a number of cases. Finally, economic factors such as unemployment, poverty, lack of, or inadequate medical/prescription coverage, as well as high out-of-pocket cost of drugs may seriously contribute to non-adherence.

Although non-adherence was often perceived as a fault of patients, and not of healthcare providers, there is evidence that healthcare system factors have an important impact on adherence (Table 3.4). Poor access to healthcare, poor drug supply, unclear information about drug administration, as well as poor follow-up and provider-patient communication and relationship may reduce the extent to which patients follow the treatment plan.

Adherence is also related to condition. Asymptomatic nature of the disease, as well as clinical improvement reduce patient motivation to take the drugs as prescribed, whereas disease severity has positive effect on adherence (Table 3.5). Patients are also less happy to take their drugs properly in both chronic, as well as psychiatric conditions.

If treatment is patient-unfriendly - e.g. due to frequent dosing, high number of prescribed medications, longer duration of treatment, drug formulation or taste of low acceptance, or adverse effects – the likelihood of patient adherence drops (Table 3.6). Certain drug classes are better adhered to compared with others (e.g. SSRIs vs other antidepressants).

Not surprisingly, many patient-related factors were found to be reported as having inconsistent impact on adherence (Table 3.7). This was particularly true for demographic factors: whereas younger age was reported to have negative impact on adherence, and older age - positive one, many studies found no relation of age and implementation of treatment regimen[16, 20, 21, 29, 38, 39, 43, 44, 48, 49]. Male gender was reported to have negative impact in some studies [37, 39, 46], and female gender - positive one [8, 25, 36, 38, 40]. However, gender was found irrelevant for adherence in many cases[6, 7, 16, 17, 20, 27, 29, 30, 43, 47, 48, 49], and a contrary effect of male gender was found with posttransplant medications[7] and with psychostymulants in children with ADHD[24]. The same was true for marital status (those married tended to have better adherence than those being single or divorced in some, but not all studies), education (better adherence with higher levels of education) and ethnicity (higher adherence in Caucasians). Patient attitudes and believes in favour of diagnosis, health recommendations and self-efficacy were closely related to adherence, as was knowledge of disease and consequences of poor adherence. On the other hand, many beliefs were found to be possible barriers for strict adherence. Poorer adherence can be expected with either drug or alcohol dependence. Finally, comorbidities and patient history had an inconsistent effect on adherence, with exception for psychiatric conditions, frequently reported to be connected with the lower rates of adherence[41, 24, 27, 34, 35, 36, 37, 79, 46].

3.4.6.2 Strengths and limitations

Our findings are similar to those of the other authors[16, 48]. However, the strength of this study is a rigorous methodology that we employed to classify literature search findings. A predefined set of criteria, and a use of well defined terminology to describe patients' deviation from prescribed treatment let us built a cohesive matrix of factors that were determinants of either adherence or non-adherence. Bearing in mind that at least 200 factors have so far been suggested to play some role in determining adherence[48], the approach adopted in our study seems to move our understanding of adherence to medication forward.

The clear distinction between *implementation* of the regimen (daily drug-taking) and *persistence* (continuity of treatment) lets us, for the first time to our knowledge, find out determinants of these two components of adherence to medication.

Finally, another strength of this systematic literature search is identification of existing gaps in our understanding of adherence. Of note is that despite broad inclusion criteria adopted for this search, we have not identified any systematic review providing determinants of adherence with short-term treatments. This undoubtedly indicates a field for further research.

The major limitation of this study was connected with the data available within the source publications that we used for this review. Most did not provide effect size of the particular determinants, thus making secondary analysis not manageable. Moreover, there might be some overlap in references of systematic reviews screened. However, as we only built a list of

determinants, and did not aim at making the meta-analysis, this possible overlap was not a source of additional bias.

3.4.6.3 Implications and recommendations

Findings of this study could be widely applied in both clinical practice, and public health, as well as suggest areas for future research.

Our analysis provides clear evidence that medication non-adherence is a summary effect of multiple determinants, belonging to several different fields. Thus, non-adherence should not be perceived as patients' fault only. To the contrary, social factors (such as social support, economic factors, etc.), healthcare-related factors (e.g. barriers to healthcare, and quality of provider-patient communication), condition characteristics, as well as therapy-related factors (such as patient friendliness of the therapy) play an important role in defining adherence. Consequently, multifaceted interventions may be the most effective answer toward unsatisfactory adherence, and its consequences. In their Cochrane review, Haynes at al.[54] observed that most of the interventions that were effective for long-term care were complex, targeting multiple adherence determinants. We believe that evidence accumulated in this study may help designing such effective interventions.

Inconsistent effect of demographic variables on patient adherence explain partly why healthcare providers are ineffective in predicting adherence in their patients[55]. In fact, their prediction rate is no better than a coin toss[56]. Neither age, gender, marital status, nor education proved to explain well the variance in patient adherence across the conditions and settings. Therefore, in order to reveal cases of non-adherence, validated tools (e.g. Morisky, or MARS questionnaires), and objective assessment methods (electronic monitoring widely accepted as a gold standard) are strongly advisable[57]. On the other hand, adherence-enhancing interventions are worth considering to implement in daily clinical practice, to be used on a regular basis for every individual patient.

Current literature is lacking reviews on determinants of adherence to short-term therapies. Having in mind high prevalence of non-adherence to short-term therapies, and especially, to antibiotics[58, 59], our findings identify this field as an important area for future research.

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3.5 Determinants of patient adherence to antihypertensive medication: a multi-national cross-sectional survey.

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3.5.1 Summary

The objective of this study was to identify the determinants of patient non-adherence to antihypertensive medication, drawing from psychosocial and economic models of behaviour. Using a cross-sectional design, 323 patients from Austria, England, Hungary, Poland and Wales in ambulatory care settings completed an online questionnaire. Adherence to medication was assessed using the Morisky (primary outcome) and MARS (secondary) scales. The percentage of patients classed as non-adherent based on self-report was found to range from 34% in Austria to 70% in Hungary. Low self efficacy (OR 0.73, 95% CI 0.68 to 0.77) and a high number of perceived barriers to taking medication (OR 2.18, 95% CI 1.64 to 2.89) were significant determinants of non-adherence across countries. 11% of the variance in non-adherence was due to country differences. This suggests patient self efficacy and perceived barriers should be key targets in the development of interventions aimed at improving adherence to antihypertensive medications. In addition interventions should be sensitive to culture and tailored to individuals' needs.

3.5.2 Introduction

Hypertension is a major risk factor for cardiovascular and cerebrovascular morbidity and mortality, with each 20 mmHg increase in systolic blood pressure associated with a doubling of the risk of death from stroke[1]. Antihypertensive treatments achieving 5-year reductions of 5-6 mmHg in blood pressure reduce coronary events by about 20% and strokes by 40%, and have contributed to the decline in cardiovascular mortality in developed countries over the last few decades[2, 3]. However adherence to antihypertensive medication remains sub-optimal. Even among patients participating in clinical studies, median persistence with antihypertensive treatment is only about one year[4]. Patients who are poorly adherent experience significantly increased risk of acute cardiovascular events, compared to those who adhere adequately[5], and incur greater healthcare costs[6]. The World Health Organisation[7] has called for further research to gain a better understanding of the determinants of non-adherence to antihypertensive medications, and to identify common risk factors for non-adherence across different countries, in order to inform strategies for improving patient adherence.

Known determinants of non-adherence may broadly be categorised to factors related to the patient (and their familial and cultural context[8]), condition, treatment, socioeconomics, and health professional / healthcare system[7, 8.]

Previous psychosocial studies have demonstrated that attitude, perceived behavioural control[9, 10]; low self efficacy[10], lack of perceived treatment utility[11]; illness perceptions[12], beliefs about medicines[13, 14] and social support[15, 16] are significantly associated with non-adherence. The current study is based on the Integrative Model of Behaviour Prediction (IMBP[17]), Leventhal's common-sense, Self-Regulatory Model[18], and McLeroy's Ecological model[19].

The IMBP integrates several earlier theories into a model that addresses not only sociocognitive aspects such as knowledge, beliefs, and attitudes towards behaviour, but also environmental factors, skills, intention/motivation, and self-efficacy. The model suggests that patients are likely to adhere to treatment if they have the necessary skills required, have a strong intention and there are no barriers to adhere. A number of studies have tested the utility of the IMBP in different populations. Abraham et al[20], for instance, found that the IMBP explained 50% of the variance in non-adherence in patients with malaria; and Barclay et al[11] found low self-efficacy and a lack of perceived treatment utility as cross-sectional determinants of non-adherence in younger, HIV-positive patients.

Lay models of health, such as the Self Regulation Model SRM[18], may provide further explanation of non-adherence. The SRM integrates social and contextual factors with the individual's cognitions and affect. The main assumption of the model is that patients' illness beliefs (illness representations) will influence their coping response which includes the management of their treatment. Illness representations include five main attributes: identity (illness label and symptoms), timeline (whether the illness is acute, cyclic, or chronic), consequences (physical, psychological or social), cause (genetic or environmental) and cure/control. The model posits that the symptoms related to the illness are important for the development of illness representations. Despite hypertension being essentially asymptomatic, a recent study found that illness representation of identity, personal control and cause explained 21% of the variance in adherence to antihypertensive medication in 227 patients[12]. Furthermore, beliefs that are inconsistent with the chronic model of illness have been shown to be associated with non-adherence in a number of patient populations[13, 14].

McLeroy's Ecological Theory[19] recognises the social environmental influences on adherence. Behaviour within ecological theory is viewed as being affected and effecting multiple levels, for example, patients' adherence will be influenced by the patient-health care provider relationship as well by interaction with family, carers, the community and society.

3.5.3 Objectives

We report on the results of a cross-sectional study of 1615 hypertensive patients, recruited from Austria, England, Hungary, Poland and Wales – countries with contrasting cultures, healthcare systems, and patient characteristics – in which the contribution of multiple, theory-driven determinants of non-adherence is tested for association with antihypertensive treatment non-adherence.

3.5.4 Method

3.5.4.1 Procedure

We invited ambulatory, adult patients with hypertension from 12 European countries to participate in an online questionnaire, however only five countries (Austria, England, Wales, Poland and Hungary) reached the target sample of 323 patients within the timeframe of the study. Recruitment was via community pharmacies (Austria, England, Wales, Poland), GP surgeries (Poland, Hungary), hypertension clinics (Hungary), advertisements placed in the press (England, Wales), and online patient support groups (Poland). The survey was administered online, anonymously through SurveyMonkey®. To reduce the chance of multiple responses, the survey was set up to allow one entry per Internet Protocol address. Patient information sheets, consent forms and eligibility checks, were provided online. Ethical approval was obtained from all relevant committees, Austria: 590/2011, Poland: OKB 03.2010, England and Wales: 10/WNo01/57, Hungary: 20457/2011-EKU (663/PI/11).

3.5.4.2 Participants

We included patients who consented, and who self-reported as being: aged 18 years or above, with ≥3 months diagnosis of hypertension and currently receiving prescribed antihypertensive medication, and personally responsible for administering their medications. Respondents declaring a psychiatric disorder or those living in a nursing home (or similar facility) were excluded.

3.5.4.3 Measures

Questions addressed potential determinants of non-adherence and included: participant demographics, use of medicines, self-rated health[21], and a battery of scales derived from economic and sociocognitive theories (see Figure 3.3).

Behaviour related to respondents' ability to afford medicines was assessed by a dichotomous question asking whether respondents had to think about the money available to spend when obtaining their medicines and six related items, each measured on a 5-point Likert scale[22]. Components of the European Social Survey[23] were used to assess household income. Participants reported their main source of income, their total annual income (in bands), whether they were coping with their present income and the ease or difficulty in borrowing money. We assessed participants' time preference (4 items) to calculate their individual discount rates in both short term (three years) and medium term (six years)[24].

The internationally standardised EUROPEP measure[25] was used to assess participants' evaluations of health care. The measure asks who mainly provides hypertensive care and their gender, and participants' level of satisfaction with the practitioner (17 items) and the practice (6 items).

We used validated, self-report tools to assess personal and sociocognitive determinants of non-adherence. Dispositional optimism was measured using the Life Orientation Test-Revised (LOT-R[26]) which contains 10 items measured on 5-point Likert scales. Illness representations were measured using the Brief Illness Perception Questionnaire (IPQ[27]) which contains 8 items that assess personal beliefs about illness consequence, timeline, personal control, treatment control, identity, concern, coherence and emotional representations (the causal subscale was removed due to translation issues). The Beliefs about Medicines Questionnaire (BMQ[28]) is an 11 item measure that assesses participants' belief in the necessity of their medication and also concerns about their medication. Components of the Theory of Planned Behaviour[29, 30] (18 items) measured attitudes/behaviours towards taking medication, subjective norms of adherence, barriers to, and facilitators of, adherence, intention to adhere and self-efficacy for adherence behaviours, each scored on a 5-point Likert scale. The Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (BRIGHT) instrument[31, 32] was used to assess environmental constraints/facilitators of adherence using two subscales: barriers (15 items) and social support (7 items).

The primary outcome measure was the Morisky questionnaire[33] which categorises participants as being non-adherent if they respond with a "yes" to at least one of four items e.g. "do you ever forget to take your high blood pressure medicine?" The Morisky questionnaire also allows for patients to be further categorised as intentionally non-adherent, based on 2 items. The Medication Adherence Rating Scale (MARS[34]) provided a secondary outcome measure of adherence. It consists of 5 items rated on a Likert scale with a low score, on a range of 5 to 25, indicating poorer levels of adherence.

Figure 3.3. Survey content and theoretical background

Questionnaire	Instrument	Theory / Factors
Demographics	*Customised items*	Distal socioeconomic
Medicines Use	*Customised items*	Distal clinical
Health status	*Stanford Self-rated Health	Distal clinical
Affordability	*Adapted questionnaire* (22)	Behavioural economics
Adherence	*4-item Morisky (33) * MARS (34)	Primary outcome measure Secondary outcome measure
Time preference	*Adapted questionnaire* (24)	Behavioural economics
Optimism	* LOT-R (26)	Proximal dispositional optimism
Beliefs	* BMQ-S11 (28)	Self-regulation beliefs about medicine/treatment
Self-efficacy	*Adapted TPB* (29,30)	Socio-cognitive theory of planned behaviour
Health service use	EUROPEP (25)	Ecological
Barriers and Social support	$BRIGHT (31,32)	IMBP: Environmental constraints/facilitators, barriers and social support
Illness perceptions	*Brief IPQ (27)	Self-regulation illness perceptions
Income	*ESS: Round 4-F31-34 (23)	Distal socioeconomic / Sociocognitive barriers

*Validated, $Validation ongoing

3.5.4.4 Translation

Measures that were not validated and available in the required language were translated and back-translated into the appropriate languages by a professional agency. The work-flow and quality management processes employed was certified to meet ISO 9001 Quality Management Standards. Forward translations was performed by highly trained, approved and accredited translators who were native speakers of the target languages and fluent in English. Back translations were performed by persons who were native English speakers and fluent in each target language. A third individual acted as a reviewer and highlighted any discrepancies between the forward and back translations and resolved them by discussion with the translators. The respective national coordinators and their teams for each participating country also proofread each translated document and provided feedback on grammatical errors. They also provided contextual interpretation of the translations to ensure that they reflected the appropriate terminology used in each participating country. In addition to this, the online survey was piloted by at least five people in each country in

order to check its technical functionality and also to check for comprehensibility, and formatting errors.

3.5.4.5 Data management

For each completing country, raw data were downloaded from SurveyMonkey® and respondents were screened for eligibility. Responses to the survey were coded in SPSS version 19 (IBM Corporation) and transferred to Stata version 10 (StataCorp LP) for imputation of missing data. Primary analyses were performed on imputed country level data sets, which were merged for cross country comparison and multilevel analysis.

3.5.4.6 Sample size

Assuming 30% of patients are classed as non-adherent by Morisky score, the sample size, based on a one-sided, 5% level of significance, is 323 completers per country.

3.5.4.7 Data analysis

We imputed missing data using chained equations in Stata[35], and created 25 data sets for each country. Analyses were performed on each set and imputation-specific coefficients were pooled according to Rubin's rules[36].

In the primary analysis, we calculated the percentage of patients classed as non-adherent according to Morisky score in each country. Potential determinants of non-adherence were initially tested univariately using chi-squared and independent samples t-tests, followed by a logistic regression with adherence as the dependent variable. We applied a bivariate method of selecting explanatory variables, whereby only variables found to be significant ($p < .05$) in the univariate analysis were entered into the regression model based on a theoretical order[37, 38]. Country comparison analysis was conducted using chi-squared tests and one way ANOVAs. We adopted a similar approach with the secondary analysis, which used MARS as the measure of adherence and in this case hierarchical linear regression was performed in which variables were entered in theoretical order, from distal to proximal determinants: demographics, followed by income and affordability, variables related to who the prescriber was, their gender, and satisfaction with the practitioner and practice, followed by optimism, illness perceptions, beliefs about medication, variables related to theory of planned behaviour, and finally barriers and use of social support.

Multilevel regression models with random intercepts and fixed effects for all determinants were specified for both Morisky (logit model) and MARS (linear regression model) in order to account for country-level variance. Determinants that were common to all countries were entered into the model. Time preference and affordability were excluded as questions differed between countries. The models for Wales were modified slightly as the BRIGHT questionnaire included one less question

given that prescriptions are free of charge in this country. Factors were removed using backwards elimination. We calculated the variance partition coefficient[39], to determine the attribution of country to the observed variance in non-adherence.

3.5.5 Results

3.5.5.1 Participants

A total of 2630 adults from 11 countries completed the questionnaire. Our analysis is restricted to the 5 countries (Austria, England, Wales, Poland and Hungary) which recruited to target sample of 323 patients within the timeframe of the study (total, 1615). Participants' characteristics in these countries are presented in Table 3.8. Those recruited from Wales tended to be older, more highly educated, and a higher proportion of females than other countries. Participants within the Hungarian sample reported more co-morbidities and took more medicines more frequently each day than other countries. A greater number of participants reported their general health as poor or fair in Poland (48.6%), Hungary (47.6%) and Austria (36.8%) than in England (19.5%) and Wales (19.8%).

Table 3.8. Demographic data and cross country comparison

Group	Subgroup	England	Wales	Poland	Hungary	Austria	*Chi sq/f*
Age	Mean (95% CI)	59.57 (58.49, 60.65)	61.05 (559.87, 62.22)	54.46 (53.16, 55.76)	58.24 (56.80, 59.67)	60.15 (58.81, 61.48)	15.89***
Gender	Male	182 (56.3%)	204 (63.2%)	152 (47.1%)	144 (44.6%)	178 (55.1%)	29.15***
	Female	141 (43.7%)	119 (36.8%)	171 (52.9%)	179 (55.4%)	145 (44.9%)	
Education	School	110 (34.0%)	98 (30.3%)	168 (52.0%)	255 (78.9%)	122 (37.8%)	199.67***
	Higher	213 (66.0%)	225 (69.7%)	155 (48.0%)	68 (21.1%)	201 (62.2%)	
Marital	Married	241 (74.6%)	259 (79.9%)	249 (77.1%)	236 (73.1%)	213 (65.9%)	18.36***
	Single/divorced/widow	82 (25.4%)	64 (19.8%)	74 (22.9%)	87 (26.9%)	110 (34.1%)	
Employment	Employed/Student	166 (51.4%)	143 (44.3%)	174 (53.9%)	124 (38.4%)	121 (37.5%)	27.56***
	Unemployed/retired etc	157 (48.6%)	180 (55.7%)	149 (46.1%)	199 (61.6%)	202 (62.5%)	
Health Status	Poor	10 (3.1%)	13 (4.0%)	24 (7.4%)	26 (8.0%)	23 (7.1%)	222.39***
	Fair	53 (16.4%)	51 (15.8%)	133 (41.2%)	128 (39.6%)	96 (29.7%)	
	Good	123 (38.1%)	116 (35.9%)	138 (42.7%)	133 (41.2%)	130 (40.2%)	
	Very good	137 (42.4%)	143 (44.3%)	28 (8.7%)	36 (11.1%)	74 (22.9%)	
Number of conditions	Mean (95% CI)	2.28 (2.15, 2.42)	2.42 (2.26, 2.57)	2.15 (2.02, 2.27)	5.17 (4.80, 5.53)	2.85 (2.59, 3.08)	13.48***

Number of different meds per day	Mean (95% CI)	3.84 (3.58, 4.10)	3.83 (3.54, 4.06)	4.11 (3.83, 4.42)	2.85 (2.68, 3.02)	4.42 (4.06, 4.79)	12.59***
Number of Tablets per day	Mean (95% CI)	4.92 (4.45, 5.40)	4.99 (4.45, 5.49)	3.28 (2.89, 3.51)	7.46 (6.90, 7.98)	5.57 (4.95, 6.07)	35.12***
Frequency of taking medications	Once a day	224 (69.3%)	241 (74.6%)	131 (40.6%)	54 (16.7%)	115 (35.6%)	328.98***
	Twice a day	63 19.5%)	47 (14.6%)	144 (44.6%)	155 (48.0%)	112 (34.6%)	
	Three or more times a day	36 (11.1%)	35 (10.8%)	48 (14.9%)	114 (35.3)	96 (29.7%)	
Income source	Salaries/wages	142 (44.0%)	135 (41.8%)	179 (55.4%)	168 (52.0%)	104 (32.2%)	30.32***
	Pensions/benefits	181 (56.0%)	188 (58.2%)	144 (44.6%)	155 (48.0%)	219 (67.8%)	
Total Income (deciles)	1-4	83 (25.7%)	92 (28.5%)	58 (18.0%)	94 (29.1%)	100 (31.0%)	86.94***
	5-7	94 (29.1%)	93 (28.8%)	79 (24.5%)	86 (35.9%)	116 (35.9%)	
	8-10	108 (33.4%)	99 (30.7%)	115 (35.5%)	61 (33.4%)	62 (19.2%)	
	Not willing to provide	38 (11.8%)	22 (6.8%)	71 (22.0%)	82 (21.1%)	45 (13.9%)	
Income perception	Living comfortably	138 (42.7%)	124 (38.4%)	0 (0%)	31 (9.6%)	71 (22.0%)	271.61***
	Coping	105 (32.5%)	125 (38.7 %)	175 (54.2%)	116 (35.9%)	152 (47.1%)	
	Difficult	55 (17.0%)	52 (16.1%)	103 (31.9%)	108 (33.4%)	57 (17.6%)	
	Not willing to provide	25 (7.7%)	22 (6.8%)	45 (13.9%)	68 (21.1%)	43 (13.3%)	
Borrowing income	Difficult	112	110	211	114	133	173.01***

		(34.7%)	(34.1%)	(65.3%)	(35.3%)	(41.2%)	
	Neither difficult or easy	73 (22.6%)	78 (24.1%)	59 (18.3%)	64 (19.8%)	93 (28.8%)	
	Easy	101 (31.3%)	91 (28.2%)	25 (7.7%)	37 (11.5%)	41 (12.7%)	
	Not willing to provide	37 (11.6%)	44 (13.6%)	28 (8.7%)	108 (33.4%)	56 (17.3%)	
Number of items prescribed	Mean (95% CI)	3.97 (3.64, 4.30)	4.23 (3.77, 4.77)	3.78 (3.30, 3.94)	4.71 (4.31, 5.07)	4.48 (4.05, 4.99)	3.92**
Affordability problem	Yes	275 (83.6%)	9 (2.8%)	221 (68.4%)	186 (57.6%)	90 (27.9%)	374.87***
	No	48 (14.2%)	314 (97.2%)	102 (31.6%)	137 (42.4 %)	233 (72.1%)	
Cost coping strategies (standardised)	Mean (95% CI)	0.15 (0.18, 0.29)	0.20 (0.06, 0.15)	0.03 (0.01, 0.07)	0.69 (0.54, 0.74)	0.36 (0.26, 0.39)	42.76***
Time preference: long	Mean (95% CI)	0.07 (0.07, 0.08)	0.04 (0.04, 0.05)	0.05 (0.04, 0.05)	-	0.09 (0.08, 0.09)	59.03***
Time preference: short	Mean (95% CI)	0.14 (0.13, 0.15)	0.09 (0.07, 0.10)	0.09 (0.08, 0.10)	-	0.18 (0.17, 0.20)	58.66***
Time preference: all	Mean (95% CI)	0.11 (0.10, 0.11)	0.06 (0.05, 0.07)	0.07 (0.06, 0.08)	-	0.14 (0.13, 0.14)	60.35***
Prescriber of medicines	GP	251 (77.7%)	248 (68.7%)	204 (63.2%)	144 (44.6%)	176 (54.5%	97.41***
	Other	72 (22.3%)	75 (21.4%)	119 (36.8%)	179 (55.4%)	147 (45.5%)	
Gender of prescriber	Male	169	138	107	147	200	35.36***

	Female	(52.3%) 154 (47.7%)	(38.4%) 185 (49.8%)	(33.1%) 216 (66.9%)	(45.5%) 176 (54.5%)	(61.9%) 123 (38.1%)	
Satisfaction with practitioner	Mean (95% CI)	67.51 (66.26, 70.15)	68.19 (66.70, 70.35)	61.29 (59.05, 64.12)	78.02 (77.91, 80.04)	69.89 (66.08, 69.17)	50.39***
Satisfaction with practice	Mean (95% CI)	21.41 (20.37, 21.79)	21.13 (20.21, 21.66)	16.17 (15.21, 16.94)	25.53 (25.35, 26.18)	23.67 (23.61, 24.78)	116.95***
Optimism	Mean (95% CI)	14.91 (14.37, 15.60)	15.23 (14.53, 15.76)	14.96 (14.64, 15.72)	14.90 (14.36, 15.32)	15.26 (14.96, 15.82)	0.62
Illness consequences	Mean (95% CI)	2.65 (2.36, 3.01)	3.12 (2.86, 3.55)	4.83 (4.43, 5.26)	5.57 (5.22, 5.94)	5.04 (4.67, 5.41)	8.32***
Timeline	Mean (95% CI)	9.24 (9.11, 6.50)	9.21 (9.10, 9.50)	9.24 (9.55, 9.84)	8.79 (8.56, 9.02)	8.78 (8.54, 9.03)	47.17***
Personal control	Mean (95% CI)	5.85 (5.36, 6.07)	5.69 (5.30, 5.96)	5.78 (5.71, 6.48)	7.10 (6.82, 7.38)	6.13 (5.73, 6.40)	11.92***
Treatment control	Mean (95% CI)	7.83 (7.51, 8.05)	7.92 (7.62, 8.17)	5.90 (5.85, 6.55)	7.84 (7.62, 8.08)	8.00 (7.74, 8.25)	13.03***
Identity	Mean (95% CI)	3.15 (2.77, 3.46)	3.26 (3.01, 3.71)	4.86 (4.41, 5.11)	4.73 (4.41, 5.06)	5.08 (4.74, 5.42)	26.77***
Concern about illness	Mean (95% CI)	5.01 (4.73, 5.43)	5.34 (5.00, 5.73)	4.08 (3.83, 4.60)	5.78 (5.46, 6.14)	5.55 (5.22, 5.93)	9.79***

Coherence	Mean (95% CI)	7.65 (7.44, 8.00)	7.87 (7.59, 8.14)	7.16 (6.87, 7.62)	8.42 (8.17, 8.65)	7.38 (7.07, 7.66)	10.08***
Emotional representations	Mean (95% CI)	3.17 (2.79, 3.55)	3.49 (3.19, 3.97)	4.44 (4.08, 4.90)	4.40 (4.08, 4.74)	4.09 (3.74, 4.40)	8.78***
Necessity of medicines	Mean (95% CI)	17.59 (17.12, 18.07)	18.14 (17.78, 18.62)	18.61 (18.51, 19.44)	19.26 (18.81, 19.69)	19.05 (18.61, 19.58)	9.09***
Concern about medicines	Mean (95% CI)	15.27 (14.68, 15.85)	15.45 (14.87, 16.08)	18.38 (17.92, 19.29)	16.01 (15.47, 16.59)	15.52 (14.97, 16.08)	18.03***
Attitude	Mean (95% CI)	28.57 (28.14, 29.12)	26.83 (26.49, 27.34)	24.14 (23.82, 24.94)	28.01 (27.76, 28.78)	27.88 (27.46, 28.63)	34.10***
Normative	Mean (95% CI)	13.03 (13.26, 13.76)	13.48 (13.33, 13.78)	11.73 (12.03, 12.74)	13.40 (13.28, 13.72)	13.13 (12.92, 13.61)	10.32***
Barriers (TPB)	Mean (95% CI)	2.22 (2.06, 2.36)	2.24 (2.11, 2.39)	2.56 (2.42, 2.77)	3.10 (2.96, 3.29)	2.07 (1.92, 2.27)	28.43***
Facilitators	Mean (95% CI)	10.26 (9.97, 10.63)	10.44 (10.24, 10.91)	11.28 (11.07, 11.81)	11.35 (11.11, 11.78)	8.12 (7.79, 8.68)	50.10***
Intention	Mean (95% CI)	9.23 (9.29, 9.55)	9.34 (9.31, 9.59)	8.23 (8.34, 8.77)	8.69 (8.57, 8.89)	9.06 (8.98, 9.39)	20.98***
Self efficacy	Mean	7.48 (7.20,	7.82 (7.58,	6.61 (6.54,	7.39 (7.13,	7.54 (7.29,	5.79***

	(95% CI)	7.73)	8.08)	7.19)	7.65)	7.82)	
Barriers (standardised)	Mean (95% CI)	0.60 (0.63, 0.78)	0.52 (0.29, 0.40)	0.49 (0.31, 0.42)	0.95 (0.99, 1.28)	0.69 (0.57, 0.70)	54.12***
Social support	Mean (95% CI)	4.08 (2.22, 3.43)	3.86 (2.75, 4.11)	6.00 (4.02, 6.58)	4.93 (4.18, 5.39)	3.65 (2.66, 3.66)	8.32***

3.5.5.2 Prevalence of non-adherence

Among the countries which reached target recruitment, patients in the Austrian sample were most adherent, with 109 (33.7%) classed as non-adherent according to the Morisky score. This was followed by patients from Wales (38.1%), England (41.5%), and Poland (57.6%). Compared to these, participants in Hungary were significantly more likely to be non-adherent (70.3%, $\chi^2 = 120.56$, $p < .001$). Intentional non-adherence ranged from 9.6% and 9.9% in Wales and England, 12.7% in Hungary, 17.3% in Austria, and 25.7% in Poland ($\chi^2 = 45.56$, $p < .001$). Non-adherence for the nine countries that recruited ≥100 hypertensive patients are presented in Figure 3.4.

Based on the secondary outcome measure (MARS), Polish participants (mean score 18.19, 95% CI = 17.77, 19.01) had significantly lower levels of adherence than those in Hungary (22.88, 95% CI = 22.74, 23.26), Austria (23.25, 95% CI = 23.03, 23.56), England (23.41, 95% CI = 23.17, 23.65), or Wales (23.46, 95% CI = 23.30, 23.77) (one way ANOVA, F (4, 1540) = 150.25, $p < .001$).

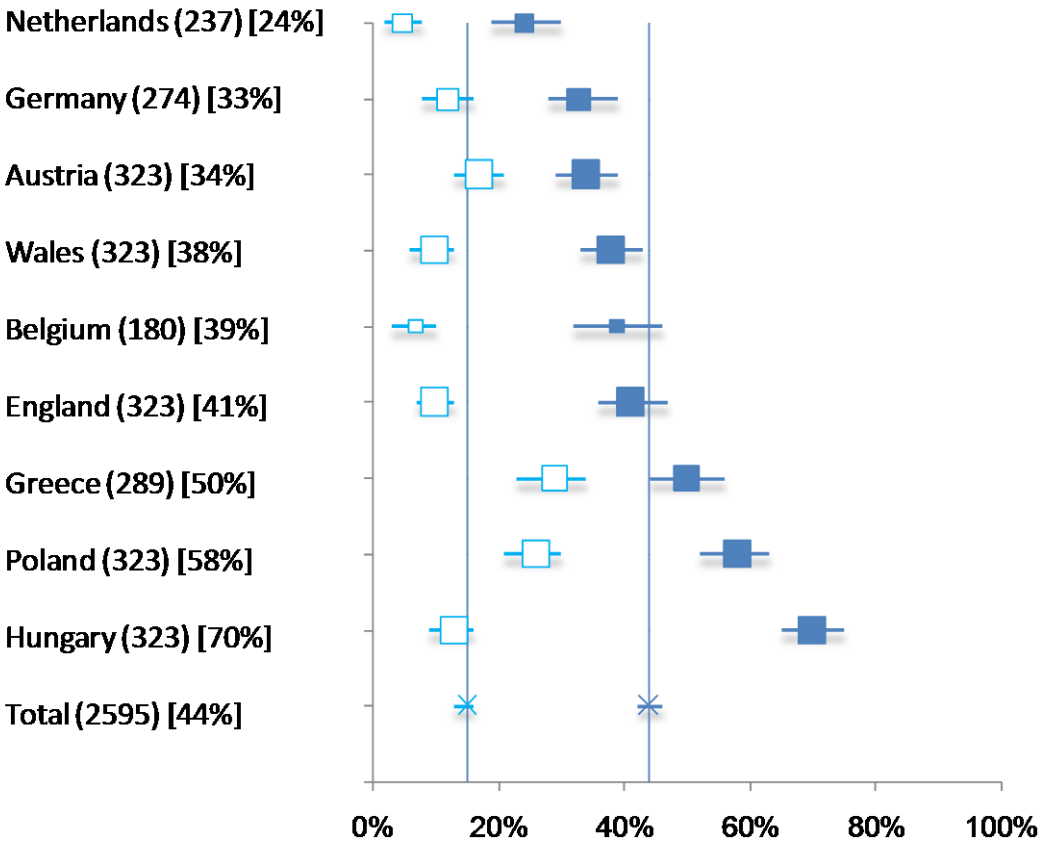

Figure 3.4. Percentage of patients classed as non-adherent (closed squares) and intentionally non-adherent (open squares) according to Morisky scores. Data are means ± 95% confidence intervals. Figures indicate the (number of respondents) and [mean percentage non-adherence].

3.5.5.3 Determinants of non-adherence

In the sample from England, employment, perceived ease and difficulty in borrowing income, number of prescribed medicines and low self efficacy were significantly associated with non-adherence (Morisky, Table 3.9). More frequent use of strategies to cope with cost (B = 0.12, SE = 0.05, beta = 0.09, p < .05) and low self-efficacy (B = -0.30, SE = 0.06, beta = -0.23, p < .001) were associated significantly with non-adherence (MARS), with the final model explaining 45% of the variance.

Table 3.9. Summary of the final logistic regression model using the Morisky as the dependent variable for England

Explanatory variables		Odds ratio	95% CI	*p* value
Age (per one year)		0.98	0.94, 1.03	0.42
Chi sq	5.45*			
Employment		3.20	1.37, 7.51	0.01**
Income source		0.96	0.34, 2.67	0.93
Income perception				
Living comfortably		0.94	0.10, 8.66	0.95
Coping		1.22	0.14, 10.93	0.86
Finding it difficult		2.80	0.31, 25.15	0.36
Borrow income				
Difficult		6.44	1.15, 36.22	0.04*
Neither difficult or easy		5.40	0.93, 31.49	0.06
Easy		5.72	1.02, 32.05	0.05*
Affordability problem		1.05	0.39, 2.81	0.99
Number of items		0.86	0.76, 0.97	0.02*
Cost coping strategies		0.96	0.96, 0.86	0.51
Chi sq	18.87			
Satisfaction with practitioner		1.01	0.99, 1.04	0.29
Satisfaction with practice		1.01	0.94, 1.08	0.80
Chi sq	0.94			
Optimism		1.00	0.93, 1.07	0.90
Chi sq	0.20			
Personal control		0.94	0.82, 1.06	0.31
Treatment control		1.02	0.84, 1.22	0.90
Coherence		0.87	0.74, 1.02	0.09
Chi sq	5.14			
Intention		0.97	0.74, 1.26	0.79
Self efficacy		0.62	0.51, 0.74	0.001***
Chi sq	42.15***			
Barriers		1.04	0.99, 1.11	0.14
Chi sq	9.63**			
Note				
* p < .05	** p < .01	*** p < .001		

In Wales, age, low personal control and low self efficacy emerged as significant in the logistic regression model for the primary outcome measure (Table 3.10). In the secondary analysis, more

frequent use of strategies to cope with cost (B = 0.69, SE = 0.11, beta = 0.33, p < .001), low intention to adhere (B = -0.34, SE = 0.16, beta = -0.25, p < .05) and low self-efficacy (B = -0.41, SE = 0.09, beta = -0.19, p < .05) were significantly associated with MARS non-adherence, with the final model accounting for 78% of the variance.

Table 3.10. Summary of the final logistic regression model using the Morisky as the dependent variable for Wales

Explanatory variables		Odds ratio	95% CI	*p* value
Age		0.97	0.94, 1.00	0.04*
Chi sq	9.71**			
Income source		0.99	0.46, 2.15	0.98
Total income				
Income deciles 1-4		2.05	0.69, 6.05	0.19
Income deciles 5-7		1.43	0.49, 4.15	0.52
Income deciles 8-10		2.92	0.97, 8.75	0.06
Chi sq	14.36**			
Satisfaction with practitioner		1.00	0.98, 1.02	0.99
Chi sq	3.45			
Optimism		1.00	0.984, 1.07	0.92
Chi sq	1.51			
Personal control		0.88	0.79, 0.99	0.03*
Coherence		1.10	0.96, 1.26	0.15
Emotional representation		0.99	0.89, 1.10	0.87
Concern about medicines		0.98	0.92, 1.06	0.65
Chi sq	1.24			
Barriers (TPB)		0.94	0.72, 1.22	0.62
Intention		0.95	0.72, 1.26	0.74
Self efficacy		0.66	0.56, 0.78	0.001***
Chi sq	41.07***			
Barriers		1.05	0.99, 1.11	0.10
Chi sq	5.67*			

Note

* p < .05 ** p < .01 *** p < .001

In Poland, low concern about illness, low self-efficacy and high number of barriers were significantly associated with the primary outcome measure of non-adherence (Table 3.11). Based on MARS, more frequent use of strategies to cope with cost (B = 0.13, SE = 0.07, beta = 0.20, p < .05) and low self efficacy (B = -0.32, SE = 0.16, beta = -0.19, p < .05) were significant. The final model accounted for only 13% of the variance in non-adherence.

Table 3.11. Summary of the final logistic regression model using the Morisky as the dependent variable for Poland

Explanatory variables		Odds ratio	95% CI	*p* value
Age		0.97	0.95, 1.01	0.13
Chi sq	0.70			
Employment		1.11	0.55, 2.26	0.77
Number of items		0.93	0.82, 1.06	0.27
Cost coping strategies		1.00	0.93, 1.07	0.89
Chi sq	6.37			
Prescriber		0.50	0.25, 1.02	0.06
Gender of prescriber		0.62	0.29, 1.31	0.21
Satisfaction with practitioner		0.99	0.97, 1.02	0.61
Satisfaction with practice		0.97	0.92, 1.03	0.38
Chi sq	6.20			
Concern (Illness)		0.80	0.69, 0.93	0.003**
Necessity (medication)		1.04	0.93, 1.16	0.54
Chi sq	1.28			
Intention		0.97	0.76, 1.23	0.79
Self efficacy		0.69	0.59, 0.81	0.001***
Chi sq	16.19***			
Barriers		1.05	1.02, 1.11	0.04*
Chi sq	2.33			

Note
* p < .05 ** p < .01 *** p < .001

In Hungary, being employed, perceived ease in borrowing money, low self-efficacy and high numbers of perceived barriers to adherence were significant for adherence based on Morisky scores (Table 3.12). In terms of our secondary outcome more frequent use of strategies to cope with cost (B = 0.22, SE = 0.03, beta = 0.29, p < .001), low perceived behavioural control (B = -0.14, SE = 0.06, beta = 0.16, p < .05), low intention (B = -0.31, SE = 0.12, beta = -0.09, p < .01), low self efficacy (B = -0.15, SE = 0.06, beta = -0.11, p < .05), high number of barriers (B = 0.07, SE = 0.02, beta = 0.33, p < .001) and high social support (B = 0.07, SE = 0.02, beta = 0.11, p < .01) were all significantly associated with non-adherence, with the final model accounting for 46% of the variance in non-adherence.

Table 3.12. Summary of the final logistic regression model using the Morisky as the dependent variable for Hungary

Explanatory variables		Odds ratio	95% CI	*p* value
Employment		3.81	1.58, 5.42	0.001***
Borrowing money		1.53		
Difficult		3.69	0.64, 2.62	0.47
Neither difficult or easy			1.34, 8.43	0.01**
Easy		1.04	0.24, 1.47	0.26
Affordability problem		0.66	0.32, 1.16	0.13
Cost coping strategies		1.03	0.97, 1.16	0.19
Chi sq (block)	24.45***			
Optimism		0.95	0.92, 1.05	0.66
Chi sq (block)	3.22			
Personal control		0.96	0.82, 1.06	0.29
Concern about meds		1.04	0.96, 1.09	0.47
Chi sq (block)	6.41*			
Self efficacy		0.84	0.73, 0.96	0.01**
Chi sq (block)	6.62**			
Barriers		1.09	1.00, 1.10	0.05*
Social support		0.97	0.99, 1.11	0.10
Chi sq (block)	10.15**			

Note
* p < .05 ** p < .01 *** p < .001

In the sample of patients from Austria, being younger, having low perceptions of illness consequences and low self-efficacy were significantly associated with non-adherence as defined by the Morisky scale (Table 3.13). Based on the MARS outcome measure, low perceptions of treatment control (B = -0.26, SE = 0.07, beta = -0.21, p < .001) and self efficacy (B = -0.28, SE = 0.06, beta = -0.26, p < .001) were significant variables, with the final model accounting for 35% of variance.

Table 3.13. Summary of the final logistic regression model using the Morisky as the dependent variable for Austria

Explanatory variables		Odds ratio	95% CI	*p* value
Age		0.96	0.93, 0.99	0.01**
No of medicines		0.88	0.74, 1.04	0.13
No of Tablets		0.97	0.87, 1.07	0.49
Chi sq	13.68***			
Employment (1)		1.30	0.55, 3.09	0.55
Income source (1)		0.72	0.31, 1.67	0.45
Number of items		1.06	0.95, 1.19	0.30
Chi sq	2.14			
Illness consequences		0.89	0.80, 0.99	0.03*
Illness timeline		0.99	0.85, 1.15	0.89
Personal control		0.93	0.84, 1.04	0.21
Treatment control		0.90	0.77, 1.04	0.16
Necessity of meds		1.03	0.94, 1.12	0.56
Chi sq	5.30			
Attitude		1.00	0.94, 1.06	0.99
Self efficacy		0.80	0.70, 0.90	0.001***
Chi sq	18.75***			
Barriers		1.04	1.00, 1.08	0.06
Social support		1.02	0.95, 1.08	0.61
Chi sq	6.18*			

Note
* p < .05 ** p < .01 *** p < .001

3.5.5.4 Multi level model

The multilevel logit model of the primary outcome identified age, employment, number of medicines, dosage frequency, normative beliefs, self-efficacy, perceived barriers, personal control, concern about illness and borrowing money to be significantly associated with non-adherence (Table 3.14). Multilevel linear regression on the secondary outcome (MARS) also found age, self-efficacy and perceived barriers to be significant, but in this instance education, and treatment control also emerged as significant. Differences between countries explained 11.4% and 26.1% of the variance in non-adherence assessed by Morisky and MARS, respectively.

Table 3.14. Summary of multilevel regression models for Morisky and MARS as outcome measures

Coefficient	Morisky			MARS		
	Odds Ratio	95% Confidence Interval		Beta Estimate	95% Confidence Interval	
Age	0.982**	0.970	0.995	.016*	.003	.028
Education				-.339*	-.655	-.023
Employment	0.633**	0.471	0.850			
Medicines number	0.881***	0.836	0.927			
Dosage frequency	1.255*	1.037	1.518			
Normative beliefs (TPB)	1.071*	1.013	1.131			
Self efficacy (TPB)	0.728***	0.684	0.774	.318***	.237	.399
Barriers (BRIGHT)	2.179***	1.643	2.890	-1.217***	-1.603	-.832
Personal control	0.933**	0.891	0.977			
Treatment control				.187***	.100	.274
Illness concern	0.935**	0.893	0.978			
Borrowing	0.869*	0.773	0.977			
Constant	32.951***	9.760	111.246	18.531***	16.591	20.471
Random effects parameters						
Between-country variance σ_u^2	0.424	0.115	0.639	2.975	0.730	12.131
Within-country-between-respondent variance σ_e^2				8.420	7.763	9.133

Note: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

For the logit model $\sigma_e^2 = \pi^2/3$

Variance partition coefficient, VPC = $\sigma_u^2/(\sigma_u^2 + \sigma_e^2)$

3.5.6 Discussion

3.5.6.1 Main findings and conclusions

Self-reported non-adherence to antihypertensive medicines is prevalent, but differs significantly across the sampled European countries (from 34% in Austria to 70% in Hungary). While a proportion of this variance is explained by country-level effects, the principal finding of the primary analysis is that low perceived self-efficacy and, to some extent, high perceived barriers and cost-relates behaviour (strategies to cope with cost of prescriptions), are consistently associated with non-adherence across all populations.

Our secondary analysis, using a multi-level model of all countries which recruited to target, was suggestive of additional determinants of non-adherence. Based on the Morisky outcome, many were not modifiable (e.g. age, employment, access to finance). However, of the potentially modifiable factors, barriers and self-efficacy were the most influential determinants, based on their effect size and statistical significance. The analysis also suggests that more appropriate and rational prescribing might achieve improvements in adherence through reduction in dosage frequency and number of prescribed medicines.

The literature on adherence to medications is dominated by analyses that test the significance of clinical (e.g. condition-specific or co-morbidity factors) and demographic characteristics as determinants of non-adherence, assuming that behaviour is a function of these characteristics, which is conceptually and empirically incorrect. Our analysis is rooted in behavioural theories to reflect the notion that individual beliefs and social influences are more relevant determinants of non-adherence than relatively fixed attributes of the person or their clinical situation. Previous studies comparable to ours in nature and size but not in scope have shown that, based on socio-cognitive and self-regulation theories, personal and perceived control[10, 12, 40], perceived benefits of treatment[38-39] and perceived barriers – such as forgetfulness and side effects[41, 42] are significant determinants of non-adherence in patients taking antihypertensive medications. Bane et al[12] identified an association between higher levels of self-efficacy and adherence in outpatients attending a hypertension clinic in Northern Ireland. Criswell et al[43] noted a similar association in a US primary care setting.

Our data provides limited evidence of a role of social support in non-adherence, with the exception of Hungary where high levels of social support was associated significantly with *non*-adherence. This contrasts with previous studies where the influence of social support on adherence has been reported[15,16].

3.5.6.2 Strengths and limitations

A key strength of this study is the range of theoretically informed factors derived from behavioural theories in both health psychology and economics which were tested concurrently across several European countries.

However there are several caveats which may limit the strength of our interpretation. First, only five of the intended twelve countries reached target recruitment, this may be due to the passive recruitment strategy and timeframe of the study. Although this did not impinge on the statistical powering, it limited our ability to generalise across different countries. Second, the different recruiting strategies may have been a significant source of heterogeneity in patients' responses. Third, as responses were elicited via self-administered, internet-based questionnaires, we had no means of confirming diagnosis and other responses, or mitigate the self-presentation bias which will reduce the external validity of our findings. Fourth, we were unable to assess for the impact of non-response bias[44] as those who failed to complete the outcome measures – which were at the beginning of the questionnaire – were prevented from progressing to the remainder of the survey. The length of the survey (155 items) represents a fifth limitation, which may have impacted on completion rates (ranging from 176 patients reaching the final question in Poland to 300 in Hungary). However, it has been suggested that content takes precedence over length in determining the appropriate use of questionnaires[45]. To reduce the potential bias of analysing complete cases, it was necessary to assume that data were missing at random. Sixth, although rooted in theory, our 'predictors' are associations, as causality cannot be inferred from cross-sectional surveys. Finally, self-reported adherence is prone to bias, with only moderate correlation with adherence measured by medication event monitoring systems[46]. Furthermore adherence measurements based on questionnaires dichotomise patients to non/adherent and over-simplifies the individuals' adherence profiles. In mitigation, we tested two outcome measures, one dichotomous, one continuous, both of which identified the significant association with self-efficacy. Although the Morisky questionnaire allowed categorisation of patients into those who were intentionally versus unintentionally non-adherent, the proportion self-reporting as intentional was too small to allow for meaningful analysis.

3.5.6.3 Implications and recommendations

The findings suggest a number of implications for the development of adherence-enhancing interventions. Most importantly, the common variables identified within the study as having strong association with non-adherence that is, self efficacy (odds ratios 0.73, 95% CI 0.68 to 0.77) and perceived barriers (OR 2.18, 95% CI 1.64 to 2.89) are amenable to change through improved communication with health care professionals or brief cognitive-behavioural intervention. Johnson et al[47] provide data in support of a model in which adherence self-efficacy mediates the relationship between positive provider interactions and adherence, however a nurse-led telephone intervention found no effect on adherence to a hypertension regimen in spite of having enhanced confidence in one's ability to adhere[48-49]. More positively, in their Cochrane reviews, Haynes et al[50] and Schroeder

et al[51] indirectly offer support for self-efficacy enhancement, as trials where supportive and individually tailored telephone calls, information on self-management, checks on understanding and concerns regarding medication, empowerment, report modest effects. They noted that evidence in relation to motivational strategies and complex interventions appear promising, but that carefully designed RCTs are necessary[51].

Our analysis suggests that a theoretically informed, controlled trial of cognitive-behavioural interventions, focused at increasing self-efficacy and reducing perceived barriers to adherence behaviours is warranted. Given the broad spectrum of potential barriers and the observation of independent, country-level differences – which may be related to cultural, health service or other factors – interventions which are tailored specifically to the population in which they are being delivered are the most likely to be effective.

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3.6 Preferences for persistence with medications: Results from a multi-national discrete choice experiment

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3.6.1 Summary

The objective of this study was to examine patients' stated preferences for persistence with medicines. A discrete choice experiment was used, which is a method rooted in random utility theory which contends that goods and services (medicines) can be described by their characteristics or attributes and that the utility (expressed as persistence) derived is a function of the various attributes. The discrete choice experiment was designed to value respondents' preferences for four attributes of hypothetical medicines: treatment benefit, dose frequency, mild adverse drug reaction (ADR) and severe ADR. 2856 patients recruited in ambulatory care settings across Austria, Belgium, England, Germany, Greece, Hungary, Netherlands, Poland and Wales completed the online questionnaire. In eight out of the nine countries, all four attributes were statistically significant in influencing patients' choice to persist with treatment ($p<0.01$). The probability of treatment benefit was not significant in Greece ($p=0.57$). Patients were most likely to persist with medications with higher treatment benefit, lower levels of dose frequency, lower risk of ADR, and lower probabilities of severe ADR. The study demonstrated that patients were willing to forego improvements in treatment benefits in order to: reduce the risk of ADR, reduce the frequency of dose, and reduce the risk of mild ADRs. They were also willing to forego reduction in risk of common, mild ADR to avoid severe (but rare) ADR and to move to a less frequent dosing schedule. With the exception of Austria ($p<0.05$), there was no evidence from other counties that self-reported adherence to antihypertensive medications influences stated preferences to persist. The results of the study suggest that in addition to treatment benefits, patients place a high value on reducing the risk of severe (but rare) ADR and frequency of dose when choosing to continue taking a medicine. Persistence is therefore associated with a willingness to trade potential benefits, harms, and convenience. As these attributes are typically in competition for individual medicines, the total utility produced by different combinations may have value in assessing patients' likelihood of persisting with medicines, and in the personalisation of medicines, or formulations thereof, to maximise persistence.

3.6.2 Introduction

Lack of persistence with medications for chronic diseases has a significant health and economic impact[1]. Consequently, there is widespread recognition that further research into the factors that influence patients' decisions not to persist with therapy is warranted[2]. Although there are a number of studies in the psychosocial and biomedical literature[3], the application of behavioural economic models to adherence to medications has been limited[4] and mainly focused on single determinants such as cost (consumer demand theory) and time (time preference)[3,5,6] [*see chapter 4*]. There has

been limited research on choice behaviour and the trade-offs patients make in their decision to continue taking a medicine over time.

The current study makes use of stated preference methods[7] with the design of a discrete choice experiment (DCE), consistent with Lancaster's economic theory of value[8]. DCE is an attribute-based survey measure in which the utility of goods and services (medicines) is described by attributes and levels. This method assumes people have clear preferences for one good over another and are able to choose between them rationally. Choices reveal information about the relative importance of each attribute, willingness to trade among attributes, and the total utility score that is generated by different combinations of these attributes. Stated preference methods represent a particularly effective method of eliciting preferences regarding health processes and outcomes, that have gained extensive use in several contexts[9,10,11]. Previous studies have successfully assessed patients' preferences for medicines using DCE[12-23], but only one study has made specific reference to adherence. In patients with type 2 diabetes Hauber et al. (2009) asked 407 respondents to indicate how likely they would be to miss or skip a dose of their preferred therapy and report that medication-related weight gain and cardiovascular risk are significant predictors of non-adherence.

3.6.3 Objectives

This study aims to explore how people value the key attributes of medicines in their decision to persist with therapy and to examine the trade-off between benefit, harm and convenience; using a discrete choice experiment within an online survey of medicines use by adult patients prescribed medication for hypertension in 11 European countries.

3.6.4 Method

3.6.4.1 Procedure

The discrete choice experiment was administered alongside the patient survey previously reported. We invited ambulatory, adult patients with hypertension from 11 European countries to participate in an online questionnaire, however only nine countries (Austria, Belgium, England, Germany, Greece, Hungary, Netherland, Poland, and Wales) reached the DCE target sample of 100 patients within the timeframe of the study. Recruitment was via community pharmacies (Austria, Belgium, England, Germany, Greece, Netherlands, Poland, Wales), GP surgeries (Poland, Hungary), hypertension clinics (Hungary), advertisements placed in the press (England, Wales), and online patient support groups (Poland). The survey was administered online, anonymously through SurveyMonkey®. To reduce the chance of multiple responses, the survey was set up to allow one entry per Internet Protocol address. Patient information sheets, consent forms and eligibility checks, were provided online. Ethical approval was obtained from all relevant committees. Further details of patient recruitment are provided in Chapter 3.2.

3.6.4.2 Participants

We included patients who consented, and who self-reported as being: aged 18 years or above, with ≥3 months diagnosis of hypertension and currently receiving prescribed antihypertensive medication, and who were personally responsible for administering their medications. Respondents declaring a psychiatric disorder or those living in a nursing home (or similar facility) were excluded.

3.6.4.3 Discrete choice experiment

Discrete choice experiments require five stages of development[9]: i) identifying attributes; ii) assigning levels; iii) experimental design; iv) collecting data; and v) data input, analysis and interpretation.

Identifying attributes: Attributes and levels included in the discrete choice experiment (Table 3.15) were derived from the literature reporting previous DCE studies[12-23] and known factors that influence adherence[25,26]. A pragmatic approach was taken to select attributes and levels that would remain meaningful across different countries, languages and medications.

Assigning levels: The choice of levels for each attribute was based on clinical evidence on the effects of commonly used treatments for the management of chronic diseases[26]; they were set at plausible values with a range sufficient to model future possibilities, encourage respondents to trade, and limit potential dominance. Each attribute was set to have the same number of levels[27].

More specifically, the DCE contained two value attributes: treatment benefit and risk of common, mild ADR, to allow comparison between attributes of benefit and harm across countries using marginal rates of substitution (MRS). Cost was not considered as an attribute due to the heterogeneity in drug pricing mechanisms and prescription charge policies across and within participating countries.

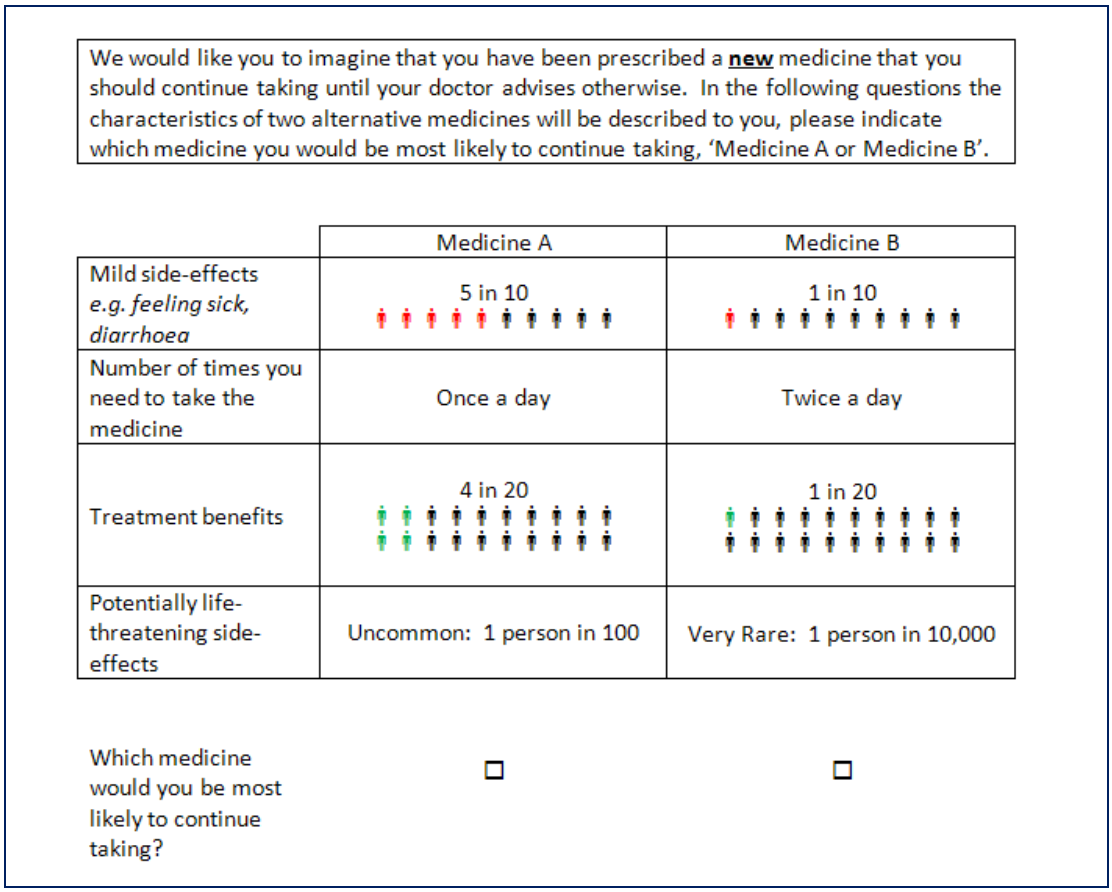
Table 3.15. Attribute names and descriptions

Attribute name	Attribute description	Level description	Level coding for analysis	Effects coding for testing
Benefit	Treatment benefits	1 in 20	5	Benefit_L0
		2 in 20	10	Benefit_L1
		4 in 20	20	Benefit_L2
Dose	Number of times you need to take the medicine	Once a day Twice a day Four times a day	Dose OD (base) _BD _QDS	Dose OD (base) _BD _QDS
Mild ADR	Mild side-effects e.g. feeling sick, diarrhoea	1 in 10 3 in 10 5 in 10	10 30 50	Mild_L0 Mild_L1 Mild_L2
Severe ADR	Potentially life-	Very rare: 1 person in 10,000	Very rare (base)	Very rare (base)

threatening side-effects	Rare: 1 person in 1,000 Uncommon: 1 person 100	_rare _uncommon	_rare _uncommon

ADR, Adverse drug reaction.

Experimental design: The number of possible questions in the DCE is given by the number of levels raised to the power of the number of attributes. A DCE with four attributes each with four levels will results in 256 possible scenarios, requiring a minimum of 128 choice sets. This would pose too great a burden on respondents, and so a fractional factorial design was selected with 9 profiles from a published design catalogue[28]. Binary choices were created using the methods of Street and Burgess (2007)[29]. The attribute and question order was randomised from that of the design catalogue, to avoid left or right hand bias. The first choice is shown in Figure 3.5. We did not include a training module.


We would like you to imagine that you have been prescribed a **new** medicine that you should continue taking until your doctor advises otherwise. In the following questions the characteristics of two alternative medicines will be described to you, please indicate which medicine you would be most likely to continue taking, 'Medicine A or Medicine B'.

	Medicine A	Medicine B
Mild side-effects *e.g. feeling sick, diarrhoea*	5 in 10	1 in 10
Number of times you need to take the medicine	Once a day	Twice a day
Treatment benefits	4 in 20	1 in 20
Potentially life-threatening side-effects	Uncommon: 1 person in 100	Very Rare: 1 person in 10,000
Which medicine would you be most likely to continue taking?	☐	☐

Figure 3.5. Example of a pair wise choice question

Details of other questions addressing potential predictors of non-adherence are presented in Chapter 3.2. These included: participant demographics, use of medicines, self-rated health[30]. Self-reported adherence was measured using the Morisky questionnaire[31] which categorises participants as being non-adherent if they respond with a "yes" to at least one of four items e.g. "do you ever forget to take your high blood pressure medicine?".

3.6.4.4 Translation

The discrete choice experiment was translated and back-translated into the appropriate languages (including a Welsh option for participants in Wales). The appropriate words to describe potentially life-threatening ADRs were identified using terminology included in Summaries of Product Characteristics, which is standardised across Europe, in which adverse reactions are listed according to frequency. The labels for frequencies of 1/100, 1/1,000 and 1/10,000 were used as levels in the experiment (Appendix 3.3).

3.6.4.5 Data management

For each completing country, raw data were downloaded from SurveyMonkey® and respondents were screened for eligibility. Responses to the survey were coded in SPSS version 19 (IBM Corporation) and transferred to Stata version 10 (StataCorp LP) for imputation of missing data. Primary analyses were performed on imputed country level data sets for all demographic and potentially interactive variables. In order to satisfy the assumptions of independent observations, missing DCE choices were not imputed and only complete cases were analysed.

3.6.4.6 Sample size

There is no formal sample size calculation for a DCE, however a minimum of 30 respondents is recommended. Assuming 30% of patients are classed as non-adherent by Morisky score, the minimum sample size was set at 100 respondents per country to enable sub-group analysis by adherence score.

3.6.4.7 Data analysis

We imputed missing demographic data using chained equations in STATA Version 10 (StataCorp LP)[32], and created 25 data sets for each country. Cross country comparisons of demographics, medicines use, and health status were performed in SPSS Version 19 on each set and imputation-specific coefficients were pooled according to Rubin's rules[33]. Country comparison analysis was conducted using chi-squared tests and one way ANOVAs of complete case data.

Results of the discrete choice experiment were analysed in STATA using a random effects logit model that allowed for repeated observations from the same respondent. Value attributes were included in the base case analysis as a linear continuous variable. We explored the assumption of linearity for frequency of dose and risk of severe ADR, using effects coding and plotting the resulting size of the attribute against the level of each attribute. The level of the base case was calculated using the estimated levels:

e.g. $\beta\_Very\ rare = -1*(\beta\_Rare + \beta\_Uncommon)$

It was hypothesised that adherence to antihypertensive medication, as assessed by the Morisky score, would affect all attributes. Subgroup analyses were therefore performed to analyse specific interactions. Log likelihood (LL) ratio tests of restricted and unrestricted models were calculated. The LL of the restricted model (base case) was compared to the sum of the LL of from the unrestricted models (adherent subgroup and non-adherent subgroup), using a 5% level of significance (6 degrees of freedom).

The marginal rates of substitution were calculated for numerical attributes to assess, for each sample, the value participants placed on each attribute relative to the probabilities of treatment benefit and common, mild ADRs. The β-coefficient for numerical attributes was for a 1% improvement; however this was re-calculated to 10% for ranking purposes as this was considered as being a more plausible increase to enable a more meaningful comparison with the categorical variables.

3.6.5 Results

3.6.5.1 Participants

A total of 2630 adults from 11 countries completed the questionnaire (Table 3.16). The discrete choice experiment analysis was restricted to nine countries that reached the target sample size and to individuals within those countries who responded to at least one of the nine choice sets within the experiment (n=2403/2586). Participants' characteristics for the countries included in the analysis are presented in Table 3.17. Country comparison using chi-squared tests and ANOVAs showed significant differences among countries for all demographics.

Table 3.16. Response and adherence rates

	Survey Response (N)	DCE Response (N)	DCE Response Rate (%)	Adherent (n)	Non-adherent (n)	Adherent (%)	Non-adherent (%)
Austria	323	312	96.59%	212	109	67.95%	32.1%
Belgium	180	165	91.67%	109	66	66.06%	33.9%
England	323	292	90.40%	185	130	63.36%	36.6%
Germany	265	248	93.58%	179	87	72.18%	27.8%
Greece	289	280	96.89%	144	144	51.43%	48.6%
Hungary	323	321	99.38%	96	226	29.91%	70.1%
Netherlands	237	207	87.34%	175	56	84.54%	15.5%
Poland	323	263	81.42%	136	176	51.71%	48.3%
Wales	323	315	97.52%	198	121	62.86%	37.1%
Total	2586	2088	80.74%				

Table 3.17. Demographic data and cross country comparison

Group	Subgroup	Austria	Belgium	England	Germany	Greece	Hungary	N'lands	Poland	Wales	*Chi sq/f*
Adherence[$]	Non-Adherent	109 (33.96%)	66 (37.71%)	130 (41.27%)	87 (32.71%)	144 (50%)	226 (70.19%)	56 (24.24%)	176 (56.41%)	121 (37.93%)	185.52***
	Adherent	212 (66.04%)	109 (62.29%)	185 (58.73%)	179 (67.29%)	144 (50%)	96 (29.81%)	175 (75.76%)	136 (43.59%)	198 (62.07%)	
Age	Mean (95% CI)	60.10 (58.77-61.43)	57.46 (55.70 – 59.21)	59.69 (58.59 – 60.78)	56.85 (55.40 – 58.31)	63.82 (62.49 – 65.15)	58.30 (56.87 – 59.74)	58.24 (59.98 – 59.50)	54.32 (53.02 – 55.63)	60.96 (59.78 – 62.14)	16.3701***
Gender	Male	177 (55.14%)	114 (65.14%)	179 (56.83%)	115 (43.23%)	115 (39.93%)	143 (44.41%)	119 (51.52%)	147 (47.12%)	200 (62.70%)	65.890***
	Female	144 (44.86%)	61 (34.86%)	136 (43.17%)	151 (56.77%)	173 (60.07%)	179 (55.59%)	112 (48.48%)	165 (52.88%)	119 (37.30%)	
Education	School	121.9 (37.98%)	6 (3.43%)	109.4 (34.73%)	48.2 (18.12%)	149.9 (52.05%)	254.0 (78.88%)	5 (2.16%)	161.7 (51.83%)	95 (29.78%)	546.644***
	Higher	199.1 (62.02%)	169 (96.57%)	205.6 (65.27%)	217.8 (81.88%)	138.1 (47.95%)	68.0 (21.12%)	226 (97.84%)	150.3 (48.17%)	224 (70.22%)	
Marital	Married	211.8 (65.98%)	132 (75.43%)	233 (73.97%)	177 (66.54%)	186.9 (64.90%)	235 (72.98%)	183.7 (79.52%)	239.6 (76.79%)	254.9 (80.59%)	37.406***
	Single/ divorced/ widow	109.2 (34.02%)	43 (24.57%)	82 (26.03%)	89 (33.46%)	101.1 (35.10%)	87 (27.02%)	47.3 (20.48%)	72.4 (23.21%)	61.4 (19.41%)	
Employment	Employed/ Student	118.6 (36.95%)	94 (53.71%)	161 (51.11%)	147.8 (55.56%)	119.3 (41.42%)	124 (38.51%)	148.8 (64.42%)	168.6 (54.04%)	142 (44.51%)	70.296***
	Unemployed/ retired etc	202.4 (63.05%)	81 (46.29%)	154 (48.89%)	118.2 (44.44%)	168.7 (58.58%)	198 (61.49%)	82.2 (35.58%)	143.4 (45.96%)	177 (55.49%)	

Group	Subgroup	Austria	Belgium	England	Germany	Greece	Hungary	N'lands	Poland	Wales	*Chi sq/f*
Health Status	Poor	23.2 (7.23%)	4 (2.29%)	10 (3.17%)	5 (1.88%)	0 (0.00%)	26 (8.07%)	4 (1.73%)	22 (7.05%)	13 (4.08%)	318.352***
	Fair	94.3 (29.38%)	25 (14.29%)	52 (16.51%)	80 (30.08%)	92.3 (32.05%)	127.2 (39.50%)	48.2 (20.87%)	129 (41.35%)	51 (15.99%)	
	Good	129.4 (40.31%)	75 (42.86%)	118 (37.46%)	139 (52.26%)	140.6 (48.82%)	132.7 (41.21%)	110.6 (47.88%)	133 (42.63%)	114.1 (35.77%)	
	Very good	74.1 (23.08%)	71 (40.57%)	135 (42.86%)	42 (15.79%)	55.1 (19.13%)	36.1 (11.21%)	68.2 (29.52%)	28 (8.97%)	140.9 (44.17%)	
Number of conditions	Mean (95% CI)	2.85 (2.59 – 3.11)	2.29 (2.10 – 2.48)	2.30 (2.16 – 2.43)	2.14 (1.98 – 2.31)	2.83 (2.62 – 3.04)	2.85 (2.68 – 3.03)	2.08 (1.92 - 2.24)	2.13 (2.01 – 2.26)	2.42 (2.26 – 2.58)	12.8779***
Number of different meds per day	Mean (95% CI)	4.41 (4.05-4.77)	3.56 (3.20 - 3.92)	3.87 (3.60 – 4.13)	3.40 (3.12 – 3.67)	4.34 (3.96 – 4.72)	5.15 (4.79 – 5.52)	3.40 (3.06 – 3.75)	4.14 (3.84 – 4.43)	3.85 (3.58 – 4.11)	11.7401***
Number of tablets per day	Mean (95% CI)	5.56 (5.00-6.13)	3.80 (3.34 – 4.25)	4.96 (4.48 – 5.44)	3.96 (3.60 – 4.33)	5.04 (4.55 – 5.52)	7.44 (6.90 – 7.98)	4.40 (3.53 – 5.26)	3.31 (2.97 – 3.65)	5.03 (4.50 – 5.55)	21.7029***
Frequency of taking medications	Once a day	114.6 (35.70%)	122.9 (70.23%)	217 (68.89%)	98 (36.84%)	51.2 (17.78%)	54 (16.77%)	154.7 (66.97%)	127.1 (40.74%)	237 (74.29%)	545.521***
	Twice a day	110 (34.27%)	33.1 (18.91%)	62 (19.68%)	125 (46.99%)	112.2 (38.96%)	155.3 (48.23%)	55.2 (23.90%)	137.5 (44.07%)	47 (14.73%)	
	Three or more times a day	96.4 (30.03%)	19 (10.86%)	36 (11.43%)	43 (16.17%)	124.6 (43.26%)	112.7 (35.00%)	21.1 (9.13%)	47.4 (15.19%)	35 (10.97%)	
Number of items prescribed	Mean (95% CI)	4.49 (4.04-4.93)	3.24 (2.87 – 3.61)	4.00 (3.66 – 4.33)	2.65 (2.38 – 2.91)	4.23 (3.85-4.62)	4.69 (4.33-5.06)	2.58 (2.29 - 2.88)	3.83 (3.53 – 4.13)	4.26 (3.78 – 4.74)	14.7883***

Group	Subgroup	Austria	Belgium	England	Germany	Greece	Hungary	N'lands	Poland	Wales	*Chi sq/f*
Income source	Salaries/wages	103 (32.09%)	107.4 (61.37%)	139.5 (44.29%)	159.6 (60.00%)	94.6 (32.85%)	167.1 (51.89%)	146.3 (63.33%)	172.3 (55.22%)	133.7 (41.91%)	78.556***
	Pensions/ benefits	218 (67.91%)	67.6 (38.63%)	175.5 (55.71%)	106.4 (40.00%)	193.4 (67.15%)	154.9 (48.11%)	84.7 (63.67%)	139.7 (44.78%)	185.3 (58.09%)	
Total Income (deciles)	1-4	100.1 (31.18%)	14.4 (8.23%)	81.4 (25.83%)	103.3 (38.83%)	137.2 (47.62%)	93.4 (29.01%)	35.6 (15.41%)	56 (17.95%)	90.5 (28.37%)	314.371***
	5-7	115.4 (35.95%)	15.4 (8.80%)	91 (28.88%)	86.7 (32.59%)	86 (29.85%)	85.3 (26.49%)	41.1 (17.79%)	76.8 (24.62%)	91 (28.53%)	
	8-10	61.5 (19.16%)	116.6 (66.63%)	106.7 (33.86%)	42 (15.79%)	31.7 (11.00%)	61 (18.94%)	110.7 (47.92%)	112.8 (36.15%)	98.9 (31.00%)	
	Not willing to provide	44 (13.71%)	28.6 (16.34%)	36 (11.42%)	34 (12.78%)	33.2 (11.52%)	82.3 (25.56%)	43.6 (18.87%)	66.4 (21.28%)	38.6 (12.10%)	

[$]Adherence data for all participants completing at least one discrete choice .

3.6.5.2 Importance and strength of attributes

Tables 3.18 to 3.26 show the results of the regression analyses for the base-case analysis. The coefficients represent the impact of a unit increase of each attribute on the probability of utility and thus persistence. The signs of the β-coefficients for statistically significant attributes were consistent across countries and with *a priori* hypotheses. All four attributes were statistically significant in eight out of the nine countries ($p<0.01$). This indicates that the probability of treatment benefit; dose frequency; risk of common, mild ADRs; and, risk of rare but severe ADRs, are all important to participants in their stated choice to continue taking a medicine, with the exception of Greece where the probability of benefit did not have a significant influence.

The positive coefficients for benefit indicate that as the probability of treatment benefit increases, participants are more likely to continue taking it (e.g. Belgium β_Benefit = 0.046; $p<0.001$). The negative coefficients for dose indicate that as dose frequency increases, participants are less likely to persist with treatment (e.g. England: β_QDS = -0.530; $p<0.001$). Participants displayed a preference for once daily dosing over two or four times a day (England: β_BD = -0.310; $p<0.001$). The negative coefficients for common, mild ADR indicate that as the probability of mild ADRs increases, participants are slightly less likely to continue taking it (e.g. Poland: β_Mild = -0.017; $p<0.001$). The negative coefficients for rare, severe ADR indicate that as the probability of potentially life threatening ADRs moves into higher risk categories, participants are less likely to persist (e.g. Germany β_uncommon = -1.491; $p<0.001$). As expected, participants displayed a preference for the probability of severe ADRs to be very rare (1 in 10,000) rather than rare (1 in 1000) or uncommon (1 in 100) (e.g. Germany β_rare = -0.688; $p<0.001$) The sizes of the coefficients in the base case regression models suggest that in the majority of countries, the sample had stronger preferences for a positive probability of treatment benefits than for a negative probability of mild ADRs (all except Germany, but this was very slightly 0.024; $p<0.001$ versus -0.025; $p<0.001$).

Table 3.18. Results of the random-effects logit regression model for Austria

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.033	0.005	0.000	0.024	0.042		-2.21
Dose OD						33.48	-74.00
_BD	-0.405	0.066	0.000	-0.534	-0.277	-12.11	26.76
_QDS	-0.715	0.069	0.000	-0.850	-0.580	-21.38	47.24
Mild ADR	-0.015	0.002	0.000	-0.018	-0.012	-0.45	
Severe ADR						15.10	-112.14
_rare	-0.490	0.063	0.000	-0.613	-0.366	-14.65	32.37
_uncommon	-1.208	0.062	0.000	-1.329	-1.087	-36.10	79.78
_cons	0.509	0.060	0.000	0.390	0.628		
No. of obs =	2847						
No. of groups =	321						
Wald chi2 (6) =	499.020						
Log likelihood =	-1527.236						

Table 3.19. Results of the random-effects logit regression model for Belgium

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.046	0.007	0.000	0.032	0.059		-1.67
Dose OD						13.34	-22.31
_BD	-0.277	0.091	0.002	-0.456	-0.097	-6.08	10.16
_QDS	-0.331	0.097	0.001	-0.520	-0.141	-7.27	12.15
Mild ADR	-0.027	0.002	0.000	-0.032	-0.023	-0.60	
Severe ADR						12.47	-66.29
_rare	-0.540	0.090	0.000	-0.717	-0.364	-11.87	19.85
_uncommon	-1.264	0.083	0.000	-1.426	-1.102	-27.77	46.44
_cons	0.443	0.073	0.000	0.299	0.586		
No. of obs =	1540						
No. of groups =	175						
Wald chi^2 (6) =	353.390						
Log likelihood =	-776.959						

Table 3.20. Results of the random-effects logit regression model for England

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.047	0.005	0.000	0.038	0.056		-1.66
Dose OD						17.89	-29.77
_BD	-0.310	0.065	0.000	-0.439	-0.182	-6.61	10.99
_QDS	-0.530	0.069	0.000	-0.666	-0.395	-11.29	18.78
Mild ADR	-0.028	0.002	0.000	-0.031	-0.025	-0.60	
Severe ADR						7.12	-44.58
_rare	-0.306	0.064	0.000	-0.432	-0.181	-6.52	10.85
_uncommon	-0.953	0.057	0.000	-1.065	-0.841	-20.28	33.74
_cons	0.321	0.053	0.000	0.217	0.425		
No. of obs =	2716						
No. of groups =	315						
Wald chi^2 (6) =	583.010						
Log likelihood =	-1439.548						

Table 3.21. Results of the random-effects logit regression model for Germany

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.024	0.006	0.000	0.013	0.035		-0.93
Dose OD						30.79	-28.68
_BD	-0.281	0.080	0.000	-0.437	-0.125	-11.86	11.05
_QDS	-0.448	0.080	0.000	-0.605	-0.291	-18.93	17.63
Mild ADR	-0.025	0.002	0.000	-0.029	-0.022	-1.07	
Severe ADR						30.13	-85.74
_rare	-0.688	0.074	0.000	-0.832	-0.544	-29.06	27.06
_uncommon	-1.491	0.069	0.000	-1.626	-1.356	-63.00	58.68
_cons	0.557	0.056	0.000	0.448	0.666		
No. of obs =	2322						
No. of groups =	266						
Wald chi^2 (6) =	600.990						
Log likelihood =	-1112.026						

Table 3.22. Results of the random-effects logit regression model for Greece

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	-0.003	0.005	0.570	-0.012	0.007		0.11
Dose OD						-368.18	-40.94
_BD	-0.222	0.073	0.002	-0.365	-0.079	80.71	8.98
_QDS	-0.790	0.067	0.000	-0.921	-0.658	287.47	31.97
Mild ADR	-0.025	0.002	0.000	-0.028	-0.021	8.99	
Severe ADR						-92.31	-51.05
_rare	-0.229	0.065	0.000	-0.356	-0.102	83.32	9.27
_uncommon	-1.032	0.057	0.000	-1.144	-0.920	375.71	41.78
_cons	0.610	0.051	0.000	0.511	0.709		
No. of obs =	2558						
No. of groups =	288						
Wald chi^2 (6) =	560.930						
Log likelihood =	-1329.795						

Table 3.23. Results of the random-effects logit regression model for Hungary

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.037	0.004	0.000	0.028	0.045		-2.25
Dose OD						18.76	-42.17
_BD	-0.204	0.061	0.001	-0.323	-0.085	-5.56	12.49
_QDS	-0.484	0.063	0.000	-0.608	-0.360	-13.20	29.68
Mild ADR	-0.016	0.001	0.000	-0.019	-0.013	-0.44	
Severe ADR						12.42	-83.66
_rare	-0.439	0.059	0.000	-0.555	-0.323	-11.98	26.93
_uncommon	-0.925	0.053	0.000	-1.030	-0.821	-25.23	56.73
_cons	0.400	0.052	0.000	0.299	0.501		
No. of obs =	2892						
No. of groups =	322						
Wald chi^2 (6) =	465.860						
Log likelihood =	-1655.287						

Table 3.24. Results of the random-effects logit regression model for Netherlands

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.041	0.006	0.000	0.030	0.053		-1.70
Dose OD						18.61	-31.56
_BD	-0.321	0.082	0.000	-0.481	-0.160	-7.79	13.21
_QDS	-0.445	0.088	0.000	-0.617	-0.274	-10.82	18.35
Mild ADR	-0.024	0.002	0.000	-0.028	-0.020	-0.59	
Severe ADR						14.25	-81.92
_rare	-0.562	0.080	0.000	-0.718	-0.406	-13.66	23.15
_uncommon	-1.426	0.080	0.000	-1.584	-1.268	-34.66	58.77
_cons	0.416	0.080	0.000	0.258	0.574		
No. of obs =	1982						
No. of groups =	231						
Wald chi^2 (6) =	422.630						
Log likelihood =	-1004.578						

Table 3.25. Results of the random-effects logit regression model for Poland

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.029	0.005	0.000	0.020	0.038		-1.70
Dose OD						39.46	-67.24
_BD	-0.335	0.067	0.000	-0.466	-0.204	-11.62	19.80
_QDS	-0.802	0.071	0.000	-0.942	-0.662	-27.84	47.44
Mild ADR	-0.017	0.002	0.000	-0.020	-0.014	-0.59	
Severe ADR						18.38	-87.63
_rare	-0.513	0.065	0.000	-0.641	-0.385	-17.79	30.32
_uncommon	-0.969	0.061	0.000	-1.088	-0.850	-33.63	57.32
_cons	0.434	0.063	0.000	0.311	0.557		
No. of obs =	2563						
No. of groups =	312						
Wald chi^2 (6) =	429.450						
Log likelihood =	-1424.027						

Table 3.26. Results of the random-effects logit regression model for Wales

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.033	0.005	0.000	0.024	0.042		-1.03
Dose OD						26.07	-26.74
_BD	-0.338	0.069	0.000	-0.473	-0.203	-10.24	10.51
_QDS	-0.523	0.068	0.000	-0.656	-0.389	-15.82	16.23
Mild ADR	-0.032	0.002	0.000	-0.035	-0.029	-0.97	
Severe ADR						14.07	-47.74
_rare	-0.432	0.065	0.000	-0.560	-0.305	-13.10	13.43
_uncommon	-1.105	0.057	0.000	-1.217	-0.992	-33.44	34.31
_cons	0.452	0.054	0.000	0.346	0.558		
No. of obs =	2857						
No. of groups =	319						
Wald chi2(6) =	672.770						
Log likelihood =	-1445.957						

3.6.5.3 Subgroup analysis

Appendix 3.4 contains the results of the regressions for the sub-group analysis by adherence category. All four attributes remained statistically significant for adherent and non-adherent samples in Austria, England, Germany, Netherlands, Poland and Wales ($p<0.01$). The results for the adherent sample suggest dose is not important in Belgium (BD p= 0.066, QDS p=0.061), Greece (BD p=0.077) and Hungary (BD p=0.10). This was also the case for the non-adherent sample in Germany (BD p=0.125) and Netherlands (BD p=0.435, QDS p=0.859). Benefit remained not significant for both samples in Greece (adherent p=0.841, non-adherent p=0.578). Log likelihood ratio tests comparing the base case 'restricted' model (all cases) with the unrestricted model for subgroups (adherent and non-adherent) indicated that in all countries, except Austria, there is no evidence that the restricted model is statistically different from the unrestricted model (Table 3.27). In Austria, the non-adherent sample had stronger preferences for probability of severe ADRs (uncommon to very rare) and dose frequency (four to once a day).

Table 3.27. Likelihood ratio test of restricted versus unrestricted models by country

Country	Log likelihood Statistic				χ2(6)
	Restricted Model	*Adherent sample*	*Non-adherent sample*	Unrestricted Model[$]	
Austria	-1527.2358	-1038.1682	-474.1814	-1512.3496	-14.8862*
Belgium	-776.9588	-496.5495	-273.1393	-769.6887	-7.2700
England	-1439.5476	-869.3357	-561.5467	-1430.8824	-8.6652
Germany	-1112.0260	-755.4037	-353.1628	-1108.5665	-3.4596
Greece	-1329.7951	-656.8962	-668.3347	-1325.2309	-4.5642
Hungary	-1655.2865	-466.8842	-1183.6113	-1650.4955	-4.7910
Netherlands	-1004.5783	-768.4440	-228.8163	-997.2602	-7.3181
Poland	-1424.0272	-611.4951	-808.9726	-1420.4676	-3.5596
Wales	-1445.9567	-869.0246	-572.4723	-1441.4969	-4.4598

[$] Sum of the log likelihood of adherence and non-adherent models
* Statistically significant at $p<0.05$

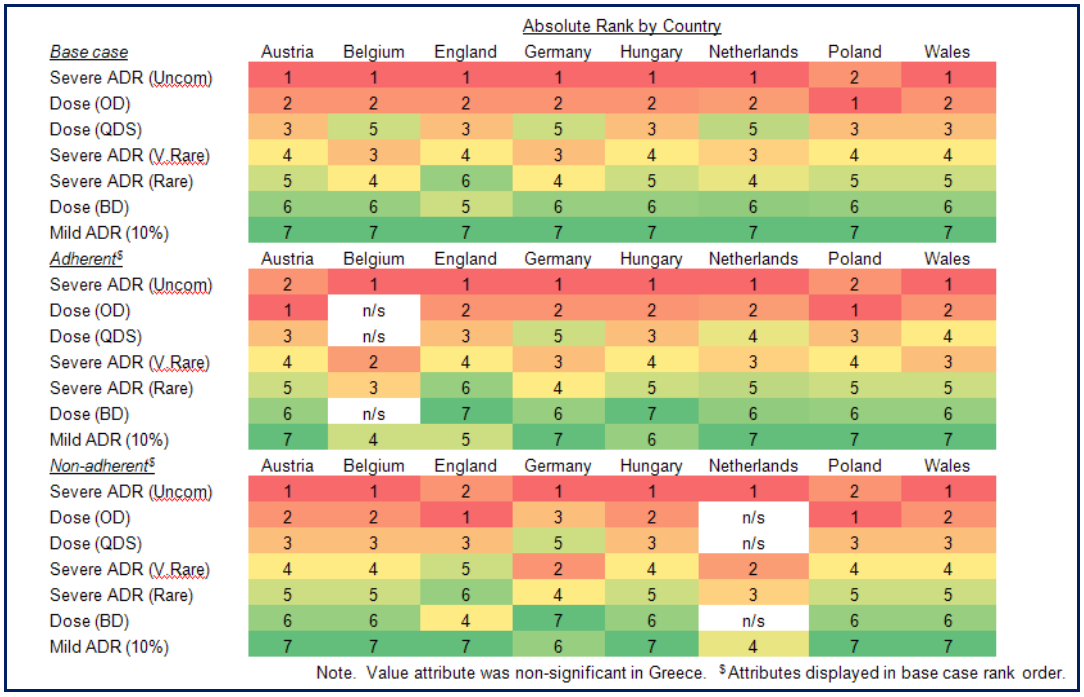
3.6.5.4 Comparing preferences

Table 3.28 presents the marginal rates of substitution (MRS) using treatment benefit as the value attribute for the base case. Participants across countries had similar preferences: the MRS values across countries suggest that patients were willing to forego improvements in treatment benefits in order to: reduce the risk of ADR (e.g. -63% Germany, -34% Netherlands, -20% England). They are also willing to give up treatment benefit to reduce the frequency of dosing (e.g. -13% Hungary to move from four times to once daily) and to reduce a fraction of the risk of mild ADRs (e.g. Wales -0.9%). They were also willing to forego a reduction in risk of mild ADR to avoid severe ADR and to move to a lower dosing schedule.

Table 3.28. Marginal rates of substitution using treatment benefit (%) as value attribute: *Base case*

Attribute	Austria	Belgium	England	Germany	Greece	Hungary	Netherlands	Poland	Wales
Dose OD	33.484 [2]	13.342 [2]	17.895	30.790	-368.182	18.755	18.615	39.456	26.067
_BD	-12.108 [6]	-6.077 [6]	-6.605	-11.860	80.708	-5.556	-7.794	-11.619	-10.244
_QDS	-21.376 [3]	-7.265 [5]	-11.290	-18.931	287.475	-13.199	-10.821	-27.837	-15.823
Mild ADR	-0.452 [7]	-0.598 [7]	-0.601	-1.074	8.992	-0.445	-0.590	-0.587	-0.975
Severe ADR	15.098 [4]	12.467 [3]	7.121	30.129	-92.309	12.423	14.246	18.378	14.070
_rare	-14.645 [5]	-11.869 [4]	-6.520	-29.056	83.317	-11.978	-13.657	-17.791	-13.095
_uncommon	-36.097 [1]	-27.772 [1]	-20.281	-62.996	375.711	-25.232	-34.664	-33.633	-33.443

The absolute rank of the MRS relative to benefit suggests preferences are similar across countries (Figure 3.6). Reduced risk of severe life-threatening ADRs is the highest ranked, followed by reduction in frequency of dose, with the exception of Poland where the top two were reversed. The probability of mild ADRs was the lowest ranked attribute with respect to benefit, and vice versa.



Absolute Rank by Country

Base case	Austria	Belgium	England	Germany	Hungary	Netherlands	Poland	Wales
Severe ADR (Uncom)	1	1	1	1	1	1	2	1
Dose (OD)	2	2	2	2	2	2	1	2
Dose (QDS)	3	5	3	5	3	5	3	3
Severe ADR (V.Rare)	4	3	4	3	4	3	4	4
Severe ADR (Rare)	5	4	6	4	5	4	5	5
Dose (BD)	6	6	5	6	6	6	6	6
Mild ADR (10%)	7	7	7	7	7	7	7	7
Adherent[$]	Austria	Belgium	England	Germany	Hungary	Netherlands	Poland	Wales
Severe ADR (Uncom)	2	1	1	1	1	1	2	1
Dose (OD)	1	n/s	2	2	2	2	1	2
Dose (QDS)	3	n/s	3	5	3	4	3	4
Severe ADR (V.Rare)	4	2	4	3	4	3	4	3
Severe ADR (Rare)	5	3	6	4	5	5	5	5
Dose (BD)	6	n/s	7	6	7	6	6	6
Mild ADR (10%)	7	4	5	7	6	7	7	7
Non-adherent[$]	Austria	Belgium	England	Germany	Hungary	Netherlands	Poland	Wales
Severe ADR (Uncom)	1	1	2	1	1	1	2	1
Dose (OD)	2	2	1	3	2	n/s	1	2
Dose (QDS)	3	3	3	5	3	n/s	3	3
Severe ADR (V.Rare)	4	4	5	2	4	2	4	4
Severe ADR (Rare)	5	5	6	4	5	3	5	5
Dose (BD)	6	6	4	7	6	n/s	6	6
Mild ADR (10%)	7	7	7	6	7	4	7	7

Note. Value attribute was non-significant in Greece. [$]Attributes displayed in base case rank order.

Figure 3.6. Relative importance of attributes relative to treatment benefit.

Tables 3.29 and 3.30 show the marginal rates of substitution using treatment benefit as the value attribute for the adherent and non-adherent sub-groups. Preferences varied slightly and inconsistently for each model. Dose frequency became the most important attribute relative to benefit in the adherent sample for Austria; and for the non-adherent sample in England. This was caused by the non-adherent sample having a smaller negative preference for severe ADRs (36% in base case to 31% in adherent model); and the non-adherent sample having a stronger preference for once a day dosing (18% in the base case to 30% in the non-adherent model), in Austria and England respectively. The change in ranks for the subgroups is illustrated in Figure 3.6.

Tables 3.31 shows the marginal rates of substitution using mild ADRs as value attribute. The marginal rates of substitution for mild ADR suggest participants are willing to give up a potential reduction in mild ADR to move from an uncommon to very rare risk of severe side-effects (e.g. Greece willing to give up a 42% improvement in risk of mild side-effects. This is followed by dose frequency, the size of this trade varied from -74% Austria to -22% Belgium.

Table 3.29. Marginal rates of substitution using treatment benefit (%) as value attribute: *Adherent sample*

Attribute	Austria	Belgium	England	Germany	Greece	Hungary	Netherlands	Poland	Wales
Dose OD	31.371	11.763	12.385	39.273	-663.809	20.458	21.181	51.462	31.400
_BD	-10.583	-5.743	-4.199	-15.019	129.627	-4.923	-8.325	-13.449	-12.944
_QDS	-20.788	-6.020	-8.186	-24.255	534.183	-15.535	-12.857	-38.013	-18.456
Mild ADR	-0.447	-0.733	-0.496	-1.143	17.109	-0.420	-0.489	-0.959	-1.241
Severe ADR	14.220	16.143	5.293	37.572	-192.433	13.637	13.229	24.804	18.846
_rare	-13.773	-15.410	-4.797	-36.429	175.324	-13.217	-12.740	-23.845	-17.605
_uncommon	-30.982	32.577	-16.687	-72.558	834.869	-29.029	-31.265	-46.943	-43.458

Table 3.30. Marginal rates of substitution using treatment benefit (%) as value attribute: *Non-adherent sample*

Attribute	Austria	Belgium	England	Germany	Greece	Hungary	Netherlands	Poland	Wales
Dose OD	38.203	14.867	29.456	18.320	-294.175	18.013	5.693	34.183	21.304
_BD	-15.123	-5.792	-11.801	-6.981	69.435	-5.781	-4.636	-10.811	-7.869
_QDS	-23.079	-9.075	-17.655	-11.339	224.740	-12.231	-1.057	-23.371	-13.435
Mild ADR	-0.439	-0.420	-0.817	-0.951	6.811	-0.452	-1.070	-0.422	-0.720
Severe ADR	15.611	8.016	10.885	19.188	-63.897	11.801	19.891	15.622	9.374
_rare	-15.172	-7.597	-10.069	-18.237	57.086	-11.349	-18.821	-15.200	-8.654
_uncommon	-44.751	-22.323	-27.801	-48.464	240.214	-23.544	-52.159	-27.906	-23.660

Table 3.31. Marginal rates of substitution using mild ADR (%) as value attribute: *Base case*

Attribute	Austria	Belgium	England	Germany	Greece	Hungary	Netherlands	Poland	Wales
Benefit	-2.210	-1.672	-1.663	-0.931	0.111	-2.248	-1.695	-1.704	-1.026
Dose OD	-74.000	-22.311	-29.766	-28.679	-40.945	-42.170	-31.560	-67.238	-26.742
_BD	26.759	10.162	10.987	11.046	8.975	12.492	13.214	19.800	10.509
_QDS	47.240	12.149	18.779	17.633	31.969	29.678	18.346	47.438	16.233
Severe ADR	-112.141	-66.287	-44.580	-85.741	-51.048	-83.663	-81.924	-87.634	-47.744
_rare	32.366	19.847	10.845	27.064	9.266	26.931	23.154	30.318	13.434
_uncommon	79.775	46.440	33.735	58.677	41.782	56.732	58.771	57.315	34.309

The absolute rank of the MRS relative to mild ADRs suggests preferences are similar across countries (Figure 3.7). Reduced risk of severe life-threatening ADRs is the most highly ranked, followed by reduction in frequency of dose. The lower rankings differ more by country when using mild ADRs as the value attribute. Comparing Figure 3.6 and Figure 3.7 suggests preferences for reduction in categorical probabilities for severe ADRs dominate across all models and that the probability of mild ADRs is the lowest ranked attribute with respect to benefit and vice versa (for the majority of samples).

Tables 3.32 and 3.33 present the marginal rates of substitution using mild ADRs as the value attribute and the estimated coefficients for the adherent and non-adherent sub-groups, respectively. Figure 3.7 illustrates how the highest rank attributes remain important in all three models: base, adherent, non-adherent (illustrated by the red band).

Absolute Rank by Country

Base case[$]	Austria	Belgium	England	Germany	Greece	Hungary	Netherlands	Poland	Wales
Severe ADR (V.Rare)	1	1	1	1	1	1	1	1	1
Severe ADR (Uncom)	2	2	2	2	2	2	2	3	2
Dose (OD)	3	3	3	3	3	3	3	2	3
Dose (QDS)	4	6	4	5	4	4	5	4	4
Severe ADR (Rare)	5	4	7	4	5	5	4	5	5
Dose (BD)	6	7	6	6	6	7	7	6	6
Benefit	7	5	5	7	n/s	6	6	7	7
Adherent[$]	Austria	Belgium	England	Germany	Greece	Hungary	Netherlands	Poland	Wales
Severe ADR (V.Rare)	1	1	1	1	1	1	1	1	1
Severe ADR (Uncom)	3	2	2	2	2	2	2	3	2
Dose (OD)	2	n/s	3	3	3	3	3	2	3
Dose (QDS)	4	n/s	5	5	4	4	4	4	4
Severe ADR (Rare)	5	3	6	4	5	5	5	5	5
Dose (BD)	6	n/s	7	7	6	7	7	6	6
Benefit	7	4	4	6	n/s	6	6	7	7
Non-adherent[$]	Austria	Belgium	England	Germany	Greece	Hungary	Netherlands	Poland	Wales
Severe ADR (V.Rare)	1	1	1	1	1	1	1	1	1
Severe ADR (Uncom)	2	2	3	2	3	2	2	3	2
Dose (OD)	3	3	2	3	2	3	n/s	2	3
Dose (QDS)	4	5	4	5	4	4	n/s	4	4
Severe ADR (Rare)	5	6	6	4	6	5	3	5	6
Benefit	7	4	7	6	n/s	6	4	7	5
Dose (BD)	6	7	5	7	5	7	n/s	6	7

[$] Attributes displayed in base case rank order.

Figure 3.7. Relative importance of attributes relative to mild ADRs.

Table 3.32. Marginal rates of substitution using mild ADR (%) as value attribute: *Adherent sample*

Attribute	Austria	Belgium	England	Germany	Greece	Hungary	Netherlands	Poland	Wales
Benefit	-2.237	-1.364	-2.014	-0.875	0.058	-2.379	-2.047	-1.043	-0.806
Dose OD	-70.167	-16.050	-24.947	-34.359	-38.799	-48.668	-43.355	-53.678	-25.306
_BD	23.671	7.836	8.458	13.139	7.577	11.712	17.039	14.029	10.432
_QDS	46.496	8.214	16.488	21.220	31.223	36.957	26.316	39.650	14.874
Severe ADR	-100.103	-65.476	-43.272	-95.350	-59.045	-100.499	-90.073	-73.836	-49.212
_rare	30.805	21.026	9.662	31.871	10.248	31.442	26.078	24.872	14.189
_uncommon	69.298	44.450	33.610	63.479	48.798	69.057	63.996	48.964	35.024

Table 3.33 Marginal rates of substitution using mild ADR (%) as value attribute: *Non-adherent sample*

Attribute	Austria	Belgium	England	Germany	Greece	Hungary	Netherlands	Poland	Wales
Benefit	-2.276	-2.384	-1.225	-1.052	0.147	-2.213	-0.935	-2.370	-1.389
Dose OD	-86.941	-35.440	-36.071	-19.264	-43.194	-39.859	-5.321	-81.005	-29.590
_BD	34.417	13.808	14.451	7.341	10.195	12.793	4.333	25.621	10.930
_QDS	52.524	21.632	21.620	11.923	32.998	27.066	0.988	55.385	18.660
Severe ADR	-136.370	-71.321	-46.376	-70.138	-43.652	-77.211	-66.339	-102.152	-44.881
_rare	34.527	18.109	12.330	19.177	8.382	25.113	17.590	36.021	12.020
_uncommon	101.843	53.212	34.045	50.961	35.271	52.099	48.749	66.131	32.862

3.6.6 Discussion

3.6.6.1 Main findings and conclusions

All four attributes significantly influenced stated preferences for continuing with medicines in 8 of the 9 national samples. Estimated coefficients for the base case and adherence subgroups suggest that: as the probability of treatment benefit increases, participants are more likely to state that they would continue with a medication; as dose frequency increases, participants are less likely to indicate that they would persist; as the probability of mild (but common) ADRs increases, participants are less likely to persist; and as the probability of potentially life threatening (and relatively rare) ADRs moves into higher risk categories, participants are less likely to persist with a medication.

There are a number of published DCEs that have successfully assessed patient preferences for different medicines[12-23]. These have variously included measures of health outcome (beneficial and/or adverse effects) and probability of outcome occurrence which define 'risk'. Patients have been shown in these studies to make trade-offs between treatment harms and the benefits associated with treatment. In their assessment of patients' preferences for characteristics associated with treatments for osteoarthritis, Ratcliffe et al.[13] reported that respondents were relatively more concerned about the risk of serious ADRs (even with a very low probability) than mild to moderate ADRs (at a much higher probability). This study is consistent with our findings. Hauber et al. (2009) reported that medication-related weight gain and cardiovascular risk has significant negative effects on likely medication adherence. The direction of effect is also consistent with that observed here, although it should be noted that our focus was on persistence with medication by patients prescribed antihypertensive treatment in Europe, whereas Hauber et al. asked how likely participants with diabetes in the UK and USA would be to miss or skip doses of medication.

In a study specifically designed to assess attitudes towards risk and patient treatment preferences, Fraenkel et al[15] concluded that patients' relative risk-attitudes are related to their treatment preferences, and that differences in risk-attitude helped explain the inter-patient variability in treatment preferences. We hypothesised that adherence to medication (concurrent behaviour) would affect persistence with medication (stated preference to continue taking a medicine); but there was no evidence that the restricted model was statistically different from the unrestricted model for the majority of countries. Only in Austria could the hypothesis be accepted at p=0.05. Further cross-country comparisons are necessary to explore influences on the selected attributes, such as the number of prescribed doses, health status, and patient demographic characteristics.

3.6.6.2 Strengths and limitations

To our knowledge this is the first study of preferences for persistence with medication to survey a large multi-national sample. The DCE was generic and used European Medicines Agency data and terminology where possible to enable general application.

There were a number of limitations. First, respondents were asked about their persistence with a hypothetical medication, which assumes they would initiate dosing of the medication described. The forced choice design confounds this as the participant has no option but to select a medicine to continue with the questionnaire which may have affected their responses. Second, it is acknowledged that trading multiple probabilities is cognitively challenging[35] although to address and hopefully minimise this, the DCE was piloted extensively and used two methods of displaying risk: (i) the pictogram was intended to aid in interpretation and also to minimise the loss of any meaning during translation. Positive and negative effects were also colour coded with green figures representing benefit and red figures portraying harm. (ii) The information was described in absolute frequencies. Literature suggests that respondents find it much easier to understand than presenting probabilities in the form of 1 in X chance[36]. The length of the survey (155 items) represents a further limitation, however it should be noted that the DCE was purposely put towards the beginning of the survey before the participant was asked to complete any items that may have conditioned their choice.

3.6.6.3 Implications and recommendations

The results of the study suggest that, in addition to treatment benefits, patients place a high value on reducing the risk of severe (but relatively rare) ADR and frequency of dose when choosing to continue taking a medicine. Persistence is therefore associated with the willingness to trade potential benefits, harms, and convenience. As these attributes are typically in competition for individual medicines, the total utility produced by different combinations may have value in assessing patients' likelihood of persisting with medicines, and in the personalisation of medicines, or formulations thereof, to maximise persistence.

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3.7 Determinants of patient adherence to short-term treatment with antibiotics: a multi national cross-sectional survey.

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3.7.1 Summary

Background: Despite symptomatic nature of these diseases, and short duration of therapy, non-adherence to antibiotics is widespread phenomenon in acute infections. Little is known on determinants of this deviation of patients from prescribed therapies. Particularly, the data on correlation between adherence to short-term, and long-term therapies are lacking.

Objectives: The aim of that study was to assess whether adherence to short-term treatment with antibiotics correlate with those to chronic treatment. Moreover, we wanted to assess the level of non-adherence to antibiotics used in ambulatory patients, as well as the determinants of this deviation from prescribed regimen.

Methods: This was a self-administered online survey based on cross-sectional design. Adult patients with hypertension from 12 European countries were invited to take part in this study. Those who admitted to take an antibiotic in an oral formulation for the treatment of short-term condition were eligible for the inclusion. Details of their antibiotic regimen, as well as adherence to antibiotics were collected with the means of an 11-item questionnaire, along with demographics, self-assessed health status, and details of respondents' economic situation.

Results: In a final analysis, data of 1354 respondents from 5 countries (Austria, England, Hungary, Poland and Wales) were included, of which 20.8% admitted being non-adherent to their last antibiotic regimen (range: Poland, 18.0% - Hungary, 27.5%). Multivariable logistic regression analysis indicated that adherence to antihypertensive treatment assessed with MARS score (OR=0.92 per unit, 95%CI: 0.88-0.97, P<0.01), and source of income for household (income from 'other sources', OR=0.47, 95%CI: 0.30-0.75, P<0.01) were associated with lower odds of admitted non-adherence to antibiotics, whereas country, higher number of daily doses, and poor feelings about household's present income were associated with self-reported non-adherence to antibiotics.

Conclusions: Only weak correlation between adherence to antibiotics, and those to chronic treatment has been found. This does not support attempts of dichotomising patients into 'generally adherent' and 'generally non-adherent'. Indirectly, this also creates the need for adherence-supporting environment, as most of the patients may be at risk of on-adherence, depending on circumstances.

3.7.2 Introduction

Antibiotics are typically prescribed for the treatment of infections. Despite symptomatic nature of these diseases, and short duration of therapy, non-adherence to antibiotics is widespread. A

metaanalysis of available studies proved that mean adherence to antibiotic therapy for acute community infections was only 62.2%[1].

The consequences of non-adherence to antibiotics include reduced treatment effectiveness, increased risk of recurrent infections, and emergence of resistant strains, as well as increased financial, and societal costs[2, 3, 4]. For that reasons, achieving patient adherence to antibiotics is important from both individual patient, as well as from public health perspective.

The aim of that study was to assess whether adherence to short-term treatment with antibiotics correlate with those to chronic treatment. Moreover, we wanted to assess the level of non-adherence to antibiotics used in ambulatory patients, as well as the determinants of this deviation from prescribed regimen. As antibiotics are most often prescribed for the treatment of community-acquired infections, it was also assumed that adherence to this class of drug may stand for a perfect exemplar of adherence to short-term treatment.

3.7.3 Subjects and methods

3.7.3.1 Procedure

We invited ambulatory, adult patients with hypertension from 12 European countries to participate in an online survey, which was administered online, anonymously through SurveyMonkey®. After answering questions focusing on adherence to chronic treatment, respondents were asked about their recent use of, and adherence to antibiotics. Details of the study procedure have been previously provided in Chapter 3.2.

Ethical approval for this study was obtained from all relevant committees, Austria: 590/2011, Poland: OKB 03.2010, England and Wales: 10/WNo01/57, Hungary: 20457/2011-EKU (663/PI/11).

3.7.3.2 Subjects

Those qualifying for inclusion in this analysis were patients from the countries that have reached the target number of responses to the primary outcome measure for entire survey study, that is to Morisky questionnaire (323), and who self-reported as being:

a) aged ≥ 18 years
b) hypertensive
c) prescribed an antibiotic in oral formulation for the treatment of short-term condition

Subjects were excluded if they admitted that they had never been prescribed an antibiotic in an oral formulation for the treatment of short-term condition, or not provided answer to the question of the time of most recent antibiotic prescription.

3.7.3.3 Questionnaire

In the lack of available validated tools specifically assessing adherence to antibiotics, an 11-item questionnaire was developed, following a conceptual framework of categories of deviation from assigned treatment that have previously been found to be the most prevalent under such circumstances[2, 5, 6]. The questionnaire comprised of 3 questions related to details of antibiotic prescription (time of the latest prescription of antibiotic in oral formulation for short-term condition, number of days that the antibiotic was scheduled for, and the number of daily doses), 4 questions assessing adherence to antibiotic (whether the patient obtained an antibiotic, initiated the treatment, completed the course of treatment, and skipped or missed any dose), and 4 questions detailing the reasons for the deviations from prescribed antibiotic therapy (one for each of the above-quoted forms of non-adherence). For details of questionnaire, see Appendix 3.5. The questionnaire was translated and back-translated into the appropriate languages (including Welsh for participants in Wales).

3.7.3.4 Definition of non-adherence with antibiotics

Respondents were defined as admitted non-adherent to antibiotics if they fulfilled at least one of the following conditions:

i. failed to obtain an antibiotic
ii. did not start the treatment with antibiotic
iii. stopped the treatment before the time scheduled by their doctor
iv. skipped or missed one or more doses

Respondents who reported not to have met any of the above conditions, were defined as adherent.

3.7.3.5 Data analysis

Data on respondents demographics, self-assessed health status, number of drugs prescribed within last 4 weeks, adherence to antihypertensive treatment, affordability and income were collected within patient survey (see Chapter 3.2 for details), and were used for this analysis, along with data on adherence to antibiotics.

In the primary analysis, we calculated the percentage of patients classed as non-adherent according to adopted definition of non-adherence to antibiotics for the whole study population. The bivariate relationship between independent explanatory variables and non-adherence to antibiotics was assessed with chi-squared statistics for categorical variables, or Kruscal-Wallis, or Manna-Whitney tests for continuous variables (age, MARS score). All statistical tests were considered significant when $P \leq 0.05$. Variables, found to be significantly associated with non-adherence, were included in

the multivariable logistic regression model. Estimates of the association between the predictors and outcome were presented with odds ratios (OR) and 95% confidence intervals (CI).

3.7.4 Results

3.7.4.1 Patient characteristics

Out of 1615 responses originally collected in 5 countries (Austria, England, Hungary, Poland, and Wales), 1354 (83,8%) met inclusion criteria, and were included in the final analysis. The number of study subjects per country ranged from 205 in Poland to 309 in Hungary. Detailed characteristics of study subjects are provided in Table 3.34. Mean age of respondents was 58.9 (11.8 SD) years, female respondents constituted 46.8% of the sample. Demographic variables differed significantly across the countries, e.g. mean age tended to be higher in Wales (60.8) and Austria (60.2) than Poland (55.0), percentage of female respondents ranged between 36.4% for Wales to 56.6% in Hungary, etc. Self-assessed health differed across the countries, as well, with much higher results for England and Wales, compared with the other countries ($P<0.005$). Economic indicators proved much better self-assessment of an economic situation of the respondents in West-European countries, compared with Poland, and Hungary.

Similarly high percentages of patients were prescribed their last antibiotic to be taken orally more than one year, and within 12 months prior to the study (42.6%, and 36.8%, respectively). However, 5.5% of respondents were taking their antibiotic during the study period. Seven days' long course of antibiotic treatment was the most prevalent option – it was admitted by 28.3% of respondents (range: 24.9% for Hungary – 33.7% for Poland). Shorter treatments stood only for 17.8% of cases. Of a note is that as many as 6.1% of total, and 12.5% of patients in Austria were prescribed antibiotics for 11-20 days. Large discrepancies in the number of antibiotic doses per day existed among the countries, with the tendency for the least frequent dosing in Austria (once-daily regimens - 38.1%, trice-daily regimens – 10.4%), and the most frequent ones in both England, and Wales (once-daily regimens – 14.6%, and 15.5%, and trice-daily regimens – 31.2%, and 35.0%, respectively).

Table 3.34. Subjects characteristics by country.

Characteristic	Total (n=1354)	Austria (n=297)	England (n=260)	Hungary (n=309)	Poland (n=205)	Wales (n=283)	P-value
Age (y)							
Average age	**58.9 (11.8 SD)**	60.2 (12.3 SD)	59.3 (9.89 SD)	58.3 (13.1 SD)	55.0 (11.6 SD)	60.8 (10.8 SD)	**P<0.001**
Gender							
Female	**633 (46.8%)**	136 (45.8%)	114 (43.9%)	175 (56.6%)	105 (51.2%)	103 (36.4%)	
Male	**721 (53.2%)**	161 (54.2%)	146 (56.1%)	134 (43.4%)	100 (48.8%)	180 (63.6%)	**P<0.001**
Education							
Primary	**182 (13.4%)**	112 (37.7%)	1 (0.4%)	62 (20.1%)	3 (1.5%)	4 (1.4%)	
Secondary	**552 (40.8%)**	113 (38.0%)	83 (31.9%)	181 (58.6%)	99 (48.3%)	76 (26.9%)	
Higher	**607 (44.8%)**	64 (21.6%)	174 (66.9%)	64 (20.7%)	103 (50.2%)	202 (71.4%)	
Not provided	**13 (1.0%)**	8 (2.7%)	2 (0.8%)	2 (0.6%)	0 (0.0%)	1 (0.3%)	**P<0.001**
Marital status							
Single	**101 (7.5%)**	34 (11.5%)	11 (4.2%)	20 (6.5%)	14 (6.8%)	22 (7.8%)	
Married/in a civil partnership	**989 (73.1%)**	189 (63.6%)	196 (75.5%)	225 (72.8%)	155 (75.6%)	224 (79.1%)	
Separated	**12 (0.9%)**	1 (0.3%)	4 (1.5%)	2 (0.7%)	2 (1.0%)	3 (1.1%)	
Divorced	**129 (9.5%)**	39 (13.1%)	38 (14.6%)	16 (5.2%)	17 (8.3%)	19 (6.7%)	
Widowed	**113 (8.3%)**	27 (9.1%)	11 (4.2%)	44 (14.2%)	16 (7.8%)	15 (5.3%)	
Not provided	**10 (0.7%)**	7 (2.4%)	0 (0.0%)	2 (0.6%)	1 (0.5%)	0 (0.0%)	**P<0.001**
Employment status							
Working full time	**427 (31.5%)**	80 (26.9%)	80 (30.8%)	97 (31.4%)	88 (42.9%)	82 (29.0%)	
Working part time	**121 (8.9%)**	17 (5.7%)	39 (15.0%)	23 (7.4%)	6 (2.9%)	36 (12.7%)	
Unemployed	**42 (3.1%)**	9 (3.0%)	9 (3.5%)	7 (2.3%)	8 (3.9%)	9 (3.2%)	
Retired	**674 (49.9%)**	171 (57.7%)	112 (43.1%)	167 (54.1%)	82 (40.0%)	142 (50.2%)	
Student	**6 (0.4%)**	0 (0%)	2 (0.8%)	1 (0.3%)	3 (1.5%)	0 (0.0%)	
On sick leave*	**19 (1.4%)**	6 (2.0%)	4 (1.5%)	5 (1.6%)	0 (0.0%)	4 (1.4%)	
Others	**54 (4.0%)**	9 (3.0%)	14 (5.4%)	7 (2.3%)	14 (6.8%)	10 (3.5%)	
Not provided	**11 (0.8%)**	5 (1.7%)	0 (0.0%)	2 (0.6%)	4 (2.0%)	0 (0.0%)	**P<0.001**
Self-assessed health status							
Excellent	**74 (5.5%)**	22 (7.4%)	17 (6.5%)	7 (2.3%)	0 (0.0%)	28 (9.9%)	
Very good	**296 (21.9%)**	47 (15.8%)	94 (36.2%)	27 (8.7%)	36 (17.6%)	92 (32.5%)	
Good	**530 (39.1%)**	116 (39.1%)	98 (37.7%)	126 (40.8%)	87 (42.4%)	103 (36.4%)	
Fair	**382 (28.2%)**	88 (29.6%)	41 (15.8%)	124 (40.1%)	82 (40.0%)	47 (16.6%)	
Poor	**69 (5.1%)**	22 (7.4%)	10 (3.8%)	25 (8.1%)	0 (0.0%)	12 (4.2%)	
Not provided	**3 (0.2%)**	2 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	**P<0.001**

Characteristic	Total (n=1354)		Austria (n=297)		England (n=260)		Hungary (n=309)		Poland (n=205)		Wales (n=283)		P-value
Number of medicines prescribed within last 4 weeks													
0	**70**	**(5.2%)**	24	(8.1%)	11	(4.2%)	11	(3.6%)	16	(7.8%)	8	(2.8%)	
1-3	**527**	**(38.9%)**	111	(37.4%)	122	(46.9%)	110	(35.6%)	62	(30.2%)	122	(43.1%)	
4-5	**295**	**(21.8%)**	53	(17.8%)	58	(22.3%)	74	(23.9%)	43	(21.0%)	67	(23.7%)	
6+	**345**	**(25.5%)**	83	(27.9%)	61	(23.5%)	93	(30.1%)	36	(17.6%)	72	(25.4%)	
Not provided	**117**	**(8.6%)**	26	(8.8%)	8	(3.1%)	21	(6.8%)	48	(23.4%)	14	(5.0%)	**P<0.001**
Out of pocket payment for medicines													
Full exemption (no co-payment)	**496**	**(36.6%)**	25	(8.4%)	174	(66.9%)	14	(4.5%)	0	(0.0%)	283	(100.0%)	
Prescription charge	**601**	**(44.4%)**	260	(87.5%)	78	(30.0%)	149	(48.2%)	114	(55.6%)	0	(0.0%)	
Full cost	**252**	**(18.6%)**	10	(3.4%)	8	(3.1%)	144	(46.6%)	90	(43.9%)	0	(0.0%)	
Not provided	**5**	**(0.4%)**	2	(0.7%)	0	(0.0%)	2	(0.7%)	1	(0.5%)	0	(0.0%)	**P<0.001**
Thinks how much money can spent on medicines													
Yes	**434**	**(32.1%)**	83	(28.0%)	37	(14.2%)	169	(54.7%)	137	(66.8%)	8	(2.8%)	
No	**814**	**(60.1%)**	212	(71.3%)	217	(83.5%)	132	(42.7%)	68	(33.2%)	185	(65.4%)	
Not provided	**106**	**(7.8%)**	2	(0.7%)	6	(2.3%)	8	(2.6%)	0	(0.0%)	90	(31.8%)	**P<0.001**
Main source of income for household													
Wages/salaries	**529**	**(39.1%)**	80	(26.9%)	109	(41.9%)	142	(45.9%)	85	(41.4%)	113	(39.9%)	
Self-employment (exc. farming)	**47**	**(3.5%)**	12	(4.0%)	16	(6.2%)	3	(1.0%)	9	(4.4%)	7	(2.5%)	
Pensions	**430**	**(31.8%)**	138	(46.5%)	103	(39.6%)	0	(0.0%)	74	(36.1%)	115	(40.6%)	
Other	**281**	**(20.7%)**	56	(18.9%)	24	(9.2%)	152	(49.2%)	8	(4.0%)	41	(14.6%)	
Not provided	**67**	**(4.9%)**	11	(3.7%)	8	(3.1%)	12	(3.9%)	29	(14.1%)	7	(2.5%)	**P<0.001**
Total income (deciles)[$]													
1 (lowest)	**67**	**(4.9%)**	24	(8.1%)	12	(4.6%)	9	(2.9%)	8	(3.9%)	14	(4.9%)	
2	**70**	**(5.2%)**	23	(7.7%)	14	(5.4%)	22	(7.1%)	0	(0.0%)	11	(3.9%)	
3	**100**	**(7.4%)**	19	(6.4%)	21	(8.1%)	25	(8.1%)	9	(4.4%)	26	(9.2%)	
4	**120**	**(8.9%)**	30	(10.1%)	18	(6.9%)	32	(10.3%)	12	(5.8%)	28	(9.9%)	
5	**138**	**(10.2%)**	46	(15.5%)	18	(6.9%)	28	(9.1%)	21	(10.2%)	25	(8.8%)	
6	**131**	**(9.7%)**	38	(12.8%)	27	(10.4%)	29	(9.4%)	10	(4.9%)	27	(9.5%)	
7	**101**	**(7.5%)**	19	(6.4%)	27	(10.4%)	21	(6.8%)	12	(5.9%)	22	(7.8%)	
8	**136**	**(10.1%)**	24	(9.1%)	33	(12.7%)	22	(7.1%)	20	(9.8%)	37	(13.1%)	

Characteristic	Total (n=1354)	Austria (n=297)	England (n=260)	Hungary (n=309)	Poland (n=205)	Wales (n=283)	P-value
9	**121 (8.9%)**	19 (6.4%)	28 (10.8%)	20 (6.5%)	24 (11.7%)	30 (10.6%)	
10 (highest)	**121 (8.9%)**	14 (4.7%)	35 (13.4%)	18 (5.8%)	28 (13.7%)	26 (9.2%)	
Not willing to provide	**201 (14.8%)**	37 (12.5%)	22 (8.5%)	79 (25.6%)	30 (14.6%)	33 (11.7%)	
Not provided	**48 (3.5%)**	4 (1.3%)	5 (1.9%)	4 (1.3%)	31 (15.1%)	4 (1.4%)	**P<0.001**
Feelings about household's present income							
Living comfortable	**325 (24.0%)**	65 (21.9%)	117 (45.0%)	30 (9.7%)	0 (0.0%)	113 (39.9%)	
Coping	**538 (39.8%)**	141 (47.5%)	84 (32.3%)	104 (33.7%)	104 (50.7%)	105 (37.1%)	
Finding it difficult	**236 (17.4%)**	54 (18.2%)	32 (12.3%)	65 (21.0%)	49 (23.9%)	36 (12.7%)	
Finding it very difficult	**76 (5.6%)**	0 (0.0%)	13 (5.0%)	36 (11.7%)	16 (7.8%)	11 (3.9%)	
Not willing to provide	**133 (9.8%)**	36 (12.1%)	12 (4.6%)	65 (21.0%)	7 (3.4%)	13 (4.6%)	
Not provided	**46 (3.4%)**	1 (0.3%)	2 (0.8%)	9 (2.9%)	29 (14.2%)	5 (1.8%)	**P<0.001**
How difficult for the respondent would be to borrow money to make ends meet in need							
Very difficult	**285 (21.0%)**	74 (24.9%)	46 (17.7%)	70 (22.7%)	46 (22.4%)	49 (17.3%)	
Quite difficult	**242 (17.9%)**	48 (16.2%)	50 (19.2%)	35 (11.3%)	60 (29.3%)	49 (17.3%)	
Neither easy nor difficult	**306 (22.7%)**	85 (28.6%)	51 (19.6%)	60 (19.4%)	40 (19.5%)	70 (24.8%)	
Quite easy	**187 (13.8%)**	23 (7.7%)	59 (22.7%)	33 (10.7%)	16 (7.8%)	56 (19.8%)	
Very easy	**68 (5.0%)**	15 (5.1%)	28 (10.8%)	0 (0.0%)	0 (0.0%)	25 (8.8%)	
Not willing to provide	**217 (16.0%)**	49 (16.5%)	23 (8.8%)	101 (32.7%)	14 (6.8%)	30 (10.6%)	
Not provided	**49 (3.6%)**	3 (1.0%)	3 (1.2%)	10 (3.2%)	29 (14.2%)	4 (1.4%)	**P<0.001**
Adherence to antihypertensive treatment as assessed with Morisky 4-item questionnaire							
Non-adherent	**644 (47.6%)**	102 (34.3%)	107 (41.2%)	218 (70.5%)	110 (53.7%)	107 (37.8%)	
Adherent	**710 (52.4%)**	195 (65.7%)	153 (58.8%)	91 (29.5%)	95 (46.3%)	176 (62.2%)	**P<0.001**
Adherence to antihypertensive treatment as assessed with MARS questionnaire							
Average MARS score	**22.9 (2.83 SD)**	23.2 (2.55 SD)	23.3 (2.61 SD)	22.7 (2.76 SD)	21.7 (3.77 SD)	23.5 (2.25 SD)	**P<0.001**
Time of the last antibiotic prescription							

Characteristic	Total (n=1354)		Austria (n=297)		England (n=260)		Hungary (n=309)		Poland (n=205)		Wales (n=283)		P-value
Up to 12 months	**499**	**(36.8%)**	139	(46.8%)	84	(32.3%)	97	(31.4%)	84	(41.0%)	95	(33.5%)	
More than 1 year ago	**577**	**(42.6%)**	99	(33.3%)	130	(50.0%)	132	(42.7%)	80	(39.0%)	136	(48.1%)	
Currently taking an antibiotic	**74**	**(5.5%)**	20	(6.7%)	12	(4.6%)	10	(3.2%)	10	(4.9%)	22	(7.8%)	
Don't remember	**204**	**(15.1%)**	39	(13.2%)	34	(13.1%)	70	(22.7%)	31	(15.1%)	30	(10.6%)	**P<0.001**
Scheduled duration of last antibiotic regimen (days)													
1-4	**57**	**(4.2%)**	18	(6.1%)	6	(2.3%)	9	(2.9%)	18	(8.8%)	6	(2.1%)	
5	**161**	**(11.9%)**	20	(6.7%)	22	(8.5%)	60	(19.4%)	28	(13.7%)	31	(11.0%)	
6	**23**	**(1.7%)**	7	(2.4%)	3	(1.1%)	4	(1.3%)	8	(3.9%)	1	(0.4%)	
7	**383**	**(28.3%)**	82	(27.6%)	81	(31.1%)	77	(24.9%)	69	(33.7%)	74	(26.1%)	
8-10	**118**	**(8.7%)**	53	(17.8%)	14	(5.4%)	16	(5.2%)	23	(11.2%)	12	(4.2%)	
11-20	**82**	**(6.1%)**	37	(12.5%)	7	(2.7%)	3	(1.0%)	20	(9.7%)	15	(5.3%)	
Not provided	**530**	**(39.1%)**	80	(26.9%)	127	(48.9%)	140	(45.3%)	39	(19.0%)	144	(50.9%)	**P<0.001**
Number of daily doses of antibiotic (times/day)													
1	**310**	**(22.9%)**	113	(38.1%)	38	(14.6%)	63	(20.4%)	52	(25.4%)	44	(15.5%)	
2	**381**	**(28.1%)**	96	(32.3%)	38	(14.6%)	118	(38.2%)	96	(56.8%)	33	(11.7%)	
3	**271**	**(20.0%)**	31	(10.4%)	81	(31.2%)	45	(14.6%)	15	(7.3%)	99	(35.0%)	
4 or more	**95**	**(7.0%)**	2	(0.7%)	37	(14.2%)	4	(1.3%)	0	(0.0%)	52	(18.4%)	
Don't remember	**269**	**(19.9%)**	46	(15.5%)	60	(23.1%)	78	(25.2%)	36	(17.6%)	49	(17.3%)	
Not provided	**28**	**(2.1%)**	9	(3.0%)	6	(2.3%)	1	(0.3%)	6	(2.9%)	6	(2.1%)	**P<0.001**

*lasting longer than 7 days $ deciles according to European Social Survey[7]

3.7.4.2 Admitted adherence to antibiotics

The total percentage of patients who admitted being non-adherent to their last antibiotic regimen was 20.8%, with a low of 18.0% for Poland, and a high of 27.5% for Hungary (P<0,05 for cross-country variability, Figure 3.8).

Only 3.0% of respondents claimed that they had not obtained their antibiotics, and only 0.7% of patients, having an antibiotic, had not started the treatment, thus standing together for *non-initiation* at the level of 3.7%. The other forms of non-adherence to antibiotics were much more prevalent: 11.1% of patient discontinued the treatment before the time scheduled by their doctor (*non-persistence*), and 6.1% admitted to omit one or more doses (poor *implementation*, see Figure 3.9 for details).

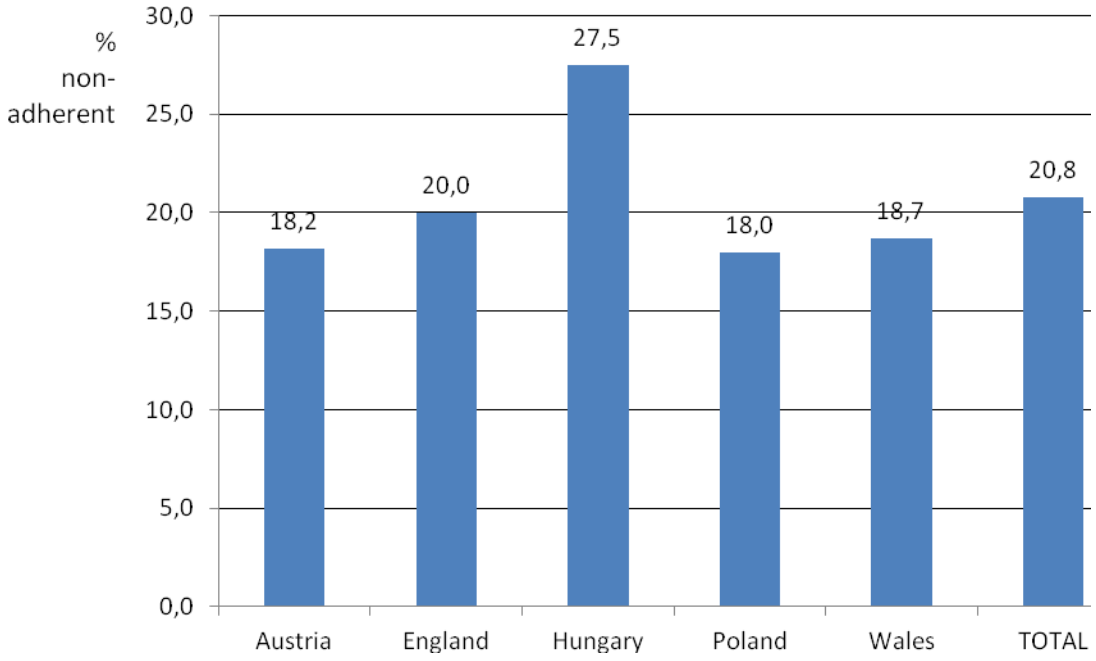

Figure 3.8
Prevalence of admitted non-adherence to antibiotics, by country.
Cross-country variability statistically significant (P<0.05).

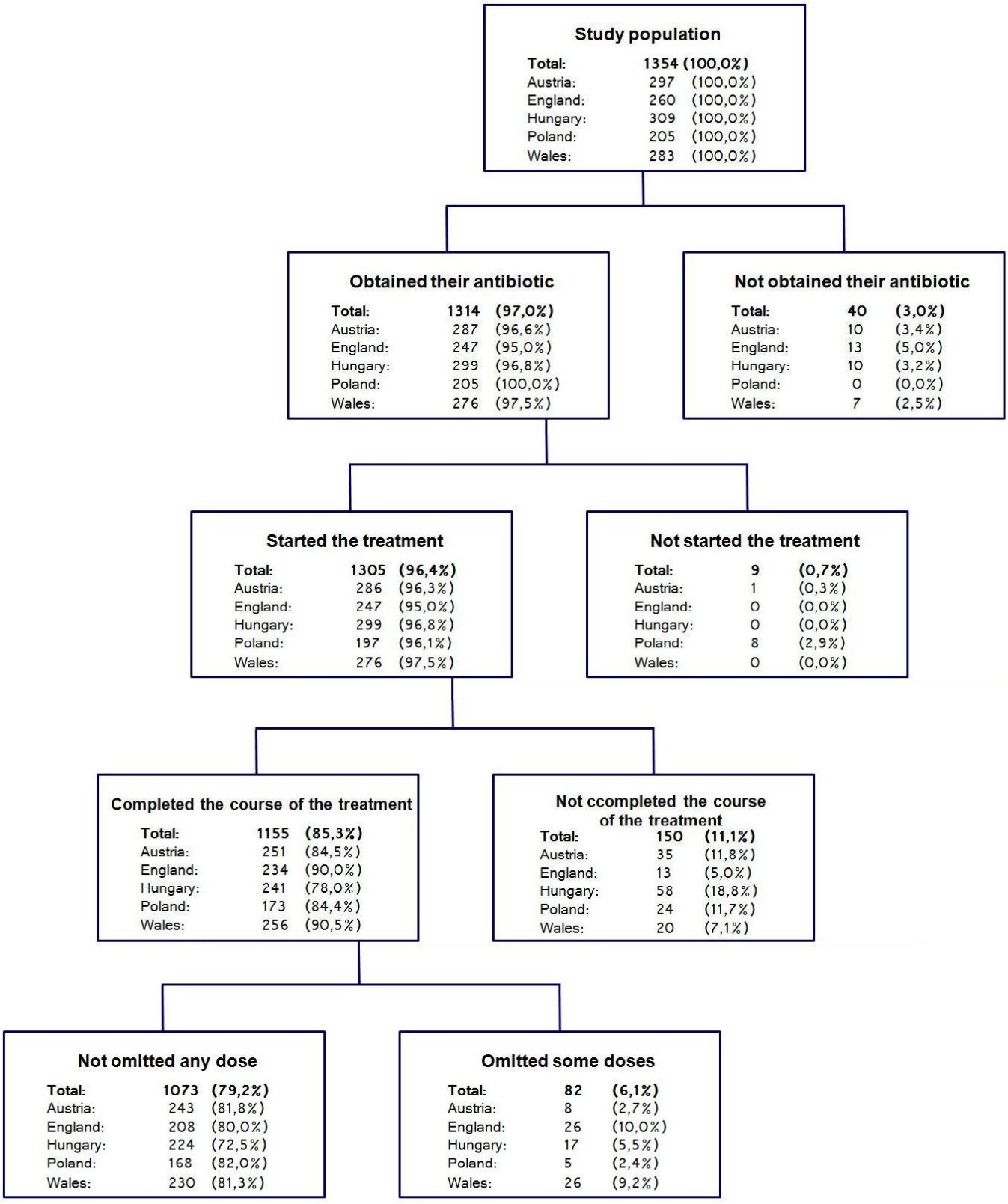

Figure 3.9

Admitted patterns of non-adherence to antibiotics in study participants. The percentages refer to the totals along the scheme.

3.7.4.3 Reasons for non-adherence to antibiotics

All the respondents who admitted not to obtain antibiotics had not provided explanation for that behaviour.

The most prevalent reasons for not initiating therapy was the expectation of side effect (3 respondents, out of 9 in total).

The reasons for not completing antibiotic treatment are provided in Table 3.35. In the majority of cases (50.7%) discontinuation was caused by feeling better. One in six patients (16.0%) admitted not to complete the course of antibiotic treatment because of side effect.

Table 3.35
Admitted reasons for not completing antibiotic treatment in those who initiated the course of treatment.

Reason	N	%
Felt better	76	50.7
Side effects	24	16.0
To save it for future	4	2.7
Cost	2	1.3
Other	13	8.7
Doesn't remember	4	2.7
Not provided	27	18.0
Total	150	100.0

Finally, the reasons for omitting one or more doses in those who admitted to complete the treatment are given in Table 3.36. In vast majority of cases (84.1%) respondents explained this with forgetfulness. Some respondents (7.3%) omitted several doses because they felt better.

Table 3.36: Admitted reasons for omitting one or more antibiotic doses in those who claimed to complete entire course of treatment.

Answer	N	%
Forgetfulness	69	84.1
Felt better	6	7.3
Side effects	2	2.4
Other	2	2.4
Doesn't remember	2	2.4
Not provided	1	1.2
Total	82	100.0

3.7.4.4 Factors associated with non-adherence to antibiotics

Univariable Analysis indicated that country, i.e. Hungary (OR=1.72, 95%CI: 1.00-2.16, P<0.01), paying full cost of prescriptions out of one's pocket (OR=1.9, 95%CI: 1.34-2.69, P<0.001), non-adherence to antihypertensive treatment assessed with Morisky score (OR=1.76, 95%CI: 1.35-2.30, P<0.001), last antibiotic prescription within previous 12 months (OR=1.36, 95%CI: 1.01-1.82, P<0.05), antibiotic to be taken three time a day (OR=1.70, 95%CI: 1.16-2.49, P<0.01), poor feelings about household's present income (finding it difficult - OR=2.01, 95%CI: 1.35-3.00, P<0.001; finding it very difficult - OR=2.02, 95%CI: 1.14-3.59, P<0.05; not willing to provide - OR=1.75, 95%CI: 1.08-2.83, P<0.05) were associated with self-reported non-adherence to antibiotics (Table 3.37). In contrast, age (OR=0.99 per year, 95%CI: 0.99-1.02, P<0.05), being retired (OR=0.64, 95%CI: 0.48-0.86, P<0.01) or other occupation (OR=0.67, 95%CI: 0.46-0.99, P<0.05; 'other occupation' included: working part time, unemployed, student, on sick leave (lasting longer than 7 days), and others (including unpaid work), adherence to antihypertensive treatment assessed with MARS score (OR=0.91 per unit, 95%CI: 0.87-0.95, P<0.001), and main source of income for household in terms of pensions (OR=0.58, 95%CI: 0.43-0.79, P<0.001), or other sources (OR=0.63, 95%CI: 0.44-0.90, P<0.05) related to lower odds of admitted non-adherence to antibiotics.

Multivariable logistic regression analysis indicated that country (i.e. Austria, OR=2.07, 95%CI: 1.16-3.47, P<0.05, and Hungary, OR=2.15, 95%CI: 1.27-3.62, P<0.01), higher number of daily doses (antibiotic to be taken three times a day, OR=1.65, 95%CI: 1.08-2.53, P<0.05), and poor feelings about household's present income (finding it difficult - OR=1.89, 95%CI: 1.18-3.01, P<0.01; not willing to provide - OR=1.85, 95%CI: 1.00-3.43, P<0.05) were associated with self-reported non-

adherence to antibiotics, whereas adherence to antihypertensive treatment assessed with MARS score (OR=0.92 per unit, 95%CI: 0.88-0.97, P<0.01), and source of income for household (income from 'other sources', OR=0.47, 95%CI: 0.30-0.75, P<0.01) were associated with lower odds of admitted non-adherence to antibiotics (Table 3.37).

Table 3.37. Logistic regression results for non-adherence to antibiotics as a dependent variable.

		Univariable logistic regression			Multivariable logistic regression		
Variable		**OR**	**95%CI**	**P-value**	**OR**	**95%CI**	**P-value**
Country	Poland	1.00			1.00		
	Austria	1.01	0.66-1.54	P>0.05	2.07	1.16-3.47	P<0.05
	England	1.14	0.72-1.78	P>0.05	1.83	0.94-3.58	P>0.05
	Hungary	1.72	1.00-2.16	P<0.01	2.15	1.27-3.62	P<0.01
	Wales	1.04	0.69-1.60	P>0.05	1.57	0.72-3.41	P>0.05
Age	(per year)	0.99	0.96-1.00	P<0.05	1.00	0.99-1.02	P>0.05
Occupation	Working full time	1.00			1.00		
	Retired	0.64	0.48-0.86	P<0.01	0.79	0.49-1.27	P>0.05
	Other[#]	0.67	0.46-0.99	P<0.05	0.68	0.44-1.27	P>0.05
Out of pocket payment for medicines	Full exemption (no co-payment)	1.00			1.00		
	Co-payment/prescription charge	0.88	0.64-1.20	P>0.05	0.75	0.44-1.27	P>0.05
	Full cost	1.90	1.34-2.69	P<0.001	1.59	0.85-2.98	P>0.05
Adherence to antihypertensive treatment as assessed with 4-item Morisky scale	Adherence	1.00			1.00		
	Non-adherence	1.76	1.35-2.30	P<0.001	1.35	0.98-1.86	P>0.05
Adherence to antihypertensive treatment as assessed with MARS scale	(per unit)	0.91	0.87-0.95	P<0.001	0.92	0.88-0.97	P<0.01
Time of the last antibiotic prescription	More than 1 year ago	1.00			1.00		
	Up to 12 months	1.36	1.01-1.82	P<0.05	1.31	0.95-1.80	P>0.05
	Currently taking an antibiotic	1.61	0.92-2.80	P>0.05	1.46	0.81-2.65	P>0.05
	Doesn't remember	0.87	0.57-1.33	P>0.05	0.85	0.52-1.41	P>0.05
Number of daily doses of antibiotic (times/day)	1	1.00			1.00		
	2	1.18	0.82-1.70	P>0.05	1.03	0.69-1.53	P>0.05

	3	1.70	1.16-2.49	P<0.01	1.65	1.08-2.53	P<0.05
	4+	1.02	0.59-1.77	P>0.05	0.94	0.49-1.81	P>0.05
	Doesn't remember	0.83	0.54-1.27	P>0.05	0.97	0.58-1.62	P>0.05
Main source of income for household	Wages/salaries	1.00			1.00		
	Self-employment (exc. farming)	0.42	0.18-1.02	P>0.05	0.51	0.20-1.27	P>0.05
	Pensions	0.58	0.43-0.79	P<0.001	0.77	0.48-1.24	P>0.05
	Other[$]	0.63	0.44-0.90	P<0.05	0.47	0.30-0.75	P<0.01
Feelings about household's present income	Living comfortable	1.00			1.00		
	Coping	1.25	0.88-1.78	P>0.05	1.30	0.88-1.91	P>0.05
	Finding it difficult	2.01	1.35-3.00	P<0.001	1.89	1.18-3.01	P<0.01
	Finding it very difficult	2.02	1.14-3.59	P<0.05	1.89	0.96-3.74	P>0.05
	Not willing to provide	1.75	1.08-2.83	P<0.05	1.85	1.00-3.43	P<0.05
How difficult for the respondent would be to borrow money to make ends meet	Very easy	1.00			1.00		
	Quite easy	1.14	0.74-1.77	P>0.05	1.27	0.75-2.15	P>0.05
	Neither easy nor difficult	0.85	0.57-1.27	P>0.05	0.97	0.60-1.58	P>0.05
	Quite difficult	0.95	0.62-1.46	P>0.05	0.98	0.59-1.63	P>0.05
	Very difficult	1.45	0.99-2.12	P>0.05	1.44	0.88-2.36	P>0.05

Legend:

[#]'Other occupation' included: working part time, unemployed, student, on sick leave (lasting longer than 7 days), and others (including unpaid work)

[$]'Other source of income included: income from farming, unemployment/redundancy benefit, any other social benefits or grants, income from investment, savings, insurance or property, and income from other sources.

3.7.5 Discussion

3.7.5.1 Main findings and conclusion

Despite symptomatic nature of acute infection, 1 in every 5 patients (20.8%) in our study admitted to be non-adherent to antibiotics, more than half of which not completed the course of treatment. Previous surveys on non-adherence to antibiotics gave similar results: 9% of patients prescribed antibiotics in accident and emergency department indicated that they had taken none of their prescribed antibiotic, and 22% of them that they had taken less than 80% of prescribed doses[8]. Another study in emergency department patients, which used two definitions of adherence (100% and ≥80% of prescribed doses), found adherence to antibiotics of 80% and 93%, respectively[9]. A survey in outpatients revealed non-adherence in 22.3% of respondents[10]. In a recent survey in Italy, 14.7% of respondents claimed to have stopped therapy early, and 5.4% modified the dosage[11]. Studies, that were based on objective electronic measurement on patient adherence, also gave similar result[12,13]. Finally, a metaanalysis of available studies proved that mean adherence to antibiotic therapy for acute community infections was only 62.2%[1].

Discontinuation was the most prevalent form of non-adherent behaviour in this study. Respondents, who stopped their therapy early, justified this with feeling better in over 50% of cases. On the other hand, in those who, having completed the full course of treatment, omitted some doses, forgetfulness was provided as the most frequent explanation (over 84% of cases). Another frequently quoted reason for either not initiation, or early discontinuation were expected, or perceived adverse effects. These patterns of behaviour were found across the studies, and seem to be the rule, not the exception[9, 12, 13].

One of the independent predictors of non-adherence with antibiotics in this study was country: both Austrian, and Hungarian respondents had their odds of non-adherence twice that high, compared with baseline. Large variability of non-adherence was observed in previous studies, as well: in multinational survey, 90% of the patients claimed to have taken the course until the end in United Kingdom, and only 53% in Thailand[14], in another one admitted non-adherence ranged from 9.9% in The Netherlands to 44.0% in China[10]. This phenomenon might be a reflection of local attitudes toward antibiotics, and culture of antibiotic use, and need further research.

We observed an effect of the number of daily doses: odds of being non-adherent rose significantly with trice-daily regimen. Similar observations were made in another studies, using objective assessment of adherence[12,15, 13], and some[10] but not all surveys[16]. Indeed, fewer daily doses, and shorter course of treatment has been found to better meet patient expectations of therapy[17].

An interesting finding of this study is the effect of economical factors on adherence to antibiotics. In this study, poorer feelings about household's present income were associated with self-reported non-adherence to antibiotics, whereas some sources of income for household were associated with lower

odds of admitted non-adherence. This finding, previously reported elsewhere low educational and socioeconomic status were associated with a higher risk of non-adherence to physician indications[11], may be important for public health.

Finally, to our knowledge, this is the first study that proves the correlation between adherence to chronic treatment and adherence to antibiotics: odds of admitted non-adherence to antibiotics were slightly lower with higher MARS scores. However, this effect, yet statistically significant, was not strong, and was not found in multivariable Analysis for another adherence measure, i.e. Morisky scale.

Patients taking their drugs on the long-term basis might be expected to easier accept, and better execute several days' long treatment with antibiotics. Indeed, in their survey Pechère et al[10] found out better adherence to antibiotics in those who were on chronic medication, and assumed that these patients ware used to taking maintenance medication.

Not surprisingly, demographic parameters, such as age, gender, education, marital status, and occupation were found not to correlate with admitted adherence to antibiotics (of which both higher age, and certain occupations positively correlated with adherence to antibiotics according to univariable regression, and not according to multivariable one). Same was true with self-assessed health status, and scheduled duration of antibiotic regimen. Noteworthy, duration of antibiotic regimen was found to have a negative impact on adherence in studies based on objective electronic assessment of patient adherence result[12, 13], and higher age positively correlated with adherence in another surveys[10, 11]. Low education was also found to have negative impact on adherence to antibiotics[11]. Another study found out that patients who were, between the others, female, employed, and better educated tended to be more compliant[9].

3.7.5.2 Strengths and limitations

The major strength of this study was the comparison of adherence to short-term treatment, and long-term one in the same patients. It is of the utmost importance that correlation of adherence to chronic treatment on adherence to antibiotics was found out with only one of the two measures of adherence with chronic treatment, employed in this study. Moreover, its effect size was only mild. Finally, MARS scale, which was the does not dichotomise patients into adherent, and non-adherent, making use of this scale less practical in a daily practice. For all these reasons, adherence to chronic therapy cannot be accepted for sure predictor of adherence to antibiotics, and vice versa.

This study shares several limitations typical for survey-based research. Of these, a recall bias is one of the most important one. This might be particularly true for those respondents (over 40%), who had to recall their use of antibiotics that took place earlier than a year prior to the study. However, numerous studies have proven that patients tend to underreport their non-adherence, rather than

overreport it. Therefore, to the reasonable extent, they may be true reporting details of their deviation from a prescribed antibiotic regimen.

3.7.5.3 Implications and recommendations

Our findings point at several factors, that are connected with non-adherence to antibiotics. The number of daily doses is the only one of them that is easily modifiable. Therefore, usage of less frequently administered antibiotics could be advocated, having in mind all the limitations of such an approach.

Important role of economic factors, as well as country, is also worth considering in designing relevant campaigns and interventions, aiming at better adherence to antiinfectives. These could be also the target for future research.

Only weak correlation between adherence to antibiotics, and those to chronic treatment has serious practical implications. From both clinical practice, as well as public health perspective, it does not support attempts of dichotomising patients into 'generally adherent' and 'generally non-adherent'. Noteworthy, a number of patients who are adherent to chronic therapy, are non-adherent to antibiotics, and vice versa, making total number of non-adherent individuals in the society even higher. This, in turn, creates the need for adherence-supporting environment, as most of patients may potentially benefit from different adherence-enhancing interventions in many ways.

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4 Application of health psychology and economic behavioural models to explain medication adherence in adult patients: a systematic review of empirical studies

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Contents

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4.1 Summary

Health psychology and economic models of patient behaviour may be used to explain medication adherence. The objective is to examine the application of health psychology and economic theory in the empirical investigation of medication adherence in adult patients; then to consolidate this evidence in a conceptual framework of determinants of adherence. A systematic review of English and non English articles using MEDLINE, EMBASE, the Cochrane Library, CINAHL, PsychINFO, and EconLit (1990-2010). Additional studies were identified by experts and scrutiny of bibliographies. Search terms relating to adherence, medicines, theory, and behavioural models were combined in two separate searches of the health psychology and economic literature. Selection of studies included all study types containing empirical data on adherence and determinants of adult medication adherence, which could be applied to a health psychology or economic theory. Data extraction involved independent extraction of articles by two reviewers using predefined data fields. Eighty-nine papers (67 health psychology, 22 economic) were included in the review. Self-report was the most common measure of adherence (n=50 studies). The extent to which individual components of the relevant model were tested varied. Health psychology models derived from social cognitive theory, self-regulation theory or social support; and, economic theories of consumer demand and time preference have been used to explain medication adherence. The majority of studies included in the review were disadvantaged by being reliant on self-reported adherence, which has been shown to deviate from objective measures of adherence; and from use of inadequate definitions. The review was restricted by date, and to adults, and did not consider behavioural models outside of the health psychology or health economic literature.

4.2 Introduction

Non-adherence to appropriately prescribed medicines is recognised as one of the major factors contributing to therapeutic non-response (0,1). It is highly prevalent, and presents a significant barrier to the safe, effective and cost-effective use of medicines. A key challenge for improving health outcomes is to develop effective adherence-enhancing interventions. A Cochrane review identified a range of interventions that improved both adherence and health outcomes (3). These included more thorough patient instructions and counselling, reminders, close follow-up, supervised self-monitoring, rewards for success, family therapy, psychological therapy, crisis intervention, and manual telephone follow-up.(3) The strategy of simplifying the dosing regimen has also shown to be effective in improving adherence (4), but uncertainty remains as to whether this putative effect translates to better health outcomes (5). Interventions identified in the Cochrane review as being clinically effective (i.e. those which improve outcome, and not just adherence) suggest that improving short-term adherence is relatively successful with a variety of simple interventions (2). However, even the most effective interventions do not lead to large, long-term improvements in adherence and treatment outcomes; this is disappointing, and probably reflects: the multiplicity of factors determining non-adherence (and hence interventions may not have been appropriate); a

complex link between adherence and outcome; an inadequate powering or follow-up of studies to detect changes in health outcome; and/or, inappropriate methods for estimating the extent of detecting non-adherence (6).

The biomedical literature is abundant with studies in which patient and disease characteristics are tested as predictors of non-adherence. These are fundamentally based on a flawed conceptual model, which assumes that behaviour such as adherence can be accurately predicted from clinical and demographic attributes, or easily measurable attributes relating to the health care system that provides patient care (7). Any behaviour–exercise, eating, smoking, medication adherence–is more likely to be determined by individual beliefs and social influences than by clinical attributes. This principle is supported by evidence from the social science literature which often shows stronger associations than studies relying on data collected for other purposes (e.g. reference 8). Consequently, a range of models of behaviour, rooted in health psychology or economic theory, have been proposed and tested empirically. A major limitation, however, is in the accurate measurement and monitoring of adherence - many studies rely on patient self-report or other methods that are potentially prone to bias and do not allow to distinguish between the three components of medication adherence (initiation, execution, discontinuation). Therefore the extent to which variability in adherence may be explained by behavioural models of adherence depends also on the accuracy, precision and reliability of the methods used in its measurement.

Studies that assess the determinants of non-adherence may help guide the development of interventions to improve adherence because they emphasise the considerations that patients themselves take into account as they decide whether to adhere to long-term treatment. This principle is particularly relevant given that non-adherence may be intentional (whether rational or irrational) as well as unintentional (e.g. based on error, such as forgetfulness; or involuntary, such as impracticality). Consolidation of behavioural models may provide a theoretical basis for the development and assessment of effective adherence-enhancing interventions.

4.3 Aims and Objectives

The aim of this work package is to develop a conceptual framework for the determinants of non-adherence. The specified objectives are:-

- To draw from the health psychology, economics and clinical therapeutics literature, models of mediation adherence;
- To consolidate the evidence on the determinants of non-adherence in a conceptual framework of patient behaviour;
- To provide a theoretical basis for the development and assessment of adherence-enhancing interventions;
- To establish a basis for long-term behaviour modification for adherence with long-term therapies;

- To establish a basis for short-term behaviour modifications for adherence with treatments of acute diseases.

In order to achieve these objectives, the following activities are planned:-

- Systematic review of the literature to find studies that have assessed the psychological and economic basis for non-adherence, together with structured models of adherence behaviour;
- Construction of models for behaviour modification relating to short- and long-term adherence, to inform the basis for development of adherence-enhancing interventions.

To examine whether models of behaviour can be used to predict medicine adherence in adult patients, we reviewed studies containing empirical data that investigated determinants of adherence in association with health psychology or economic theory.

4.4 Method

The report of this systematic review follows the PRISMA statement (9).

4.4.1 Protocol and registration

Search strategies and inclusion criteria were specified in advance of the review and documented in a review protocol. This was developed in consultation with partners assigned to this work package. Partners of the project were also involved in the screening of the titles and abstracts and the retrieval of papers.

4.4.2 Eligibility criteria

Types of studies: Empirical studies that investigate the association between the determinants of adherence, based on health psychology or economics theory, and patients' medication adherence.
Types of participants: Adult patients (>= 18 years) prescribed medicines for any condition. Complimentary medicines were excluded from the review. Studies looking at medicines adherence in children were excluded because their adherence is not exclusive to their behaviour; and, the health psychology and behavioural economics in this field, predominately focuses on adults.
Types of outcome measures: To be included in the review, the study had to include at least one measure of adherence (figure 4.1). Studies that did not quantify adherence were excluded. All potential measures of determinants were included.

Direct methods of adherence measurement
Directly observed therapy (DOT)
Therapeutic drug monitoring (TDM)
Measurement of biologic marker in the blood
Indirect methods of adherence measurement
Electronic compilation of drug dosing histories
Counts of returned tablets / untaken dosage forms
Prescription records / audits of prescription refills
Self report patient questionnaires and diaries
Assessment of patients' clinical responses and/or physiological marker or effect

Figure 4.1: Methods of measuring / monitoring adherence

4.4.3 Information sources

Studies published in peer reviewed journals between 01/01/1990 and 01/01/2010 were identified by searching electronic databases, scrutinising reference lists of articles, and in consultation with partners. No language restrictions were imposed, non English papers were translated. The search was applied to: MEDLINE via Pubmed, EMBASE, the Cochrane Library, CINAHL, PsychINFO, and EconLit. The last search was conducted on 2 March 2010.

4.4.4 Search

Two separate search strategies were used to independently search for health psychology (appendix 4.1) and economic papers (appendix 4.2). Both combined terms relating to 'adherence', 'medicines', 'models' and 'specific theories'. Health psychology and economic theories were identified using text books and through consultations with experts. This was supplemented with the catch-all truncated terms psycholog* or economic*.

For consistency within the ABC project, the search strategies used to identify adherence papers in work package one 10 [taxonomy and terminology of patient adherence] was also used in this work package. These search terms for adherence had been coded according to the indexing system specific to each database. "MeSH terms" were used in MEDLINE and in The Cochrane Library. The "EMTREE tools" were used in EMBASE.

The final search strategies were reviewed by ABC partners assigned to this work package.

Inclusion criteria:

All papers containing empirical data on medication adherence in adult patients; that is used to investigate determinants to adherence, which could be associated with a health psychology or economic theory. Articles published in a peer-reviewed journal between 01/01/1990 and 01/01/2010.

Exclusion criteria:

1. Publication type: non-peer reviewed articles (e.g. editorials, letters) or literature (e.g. conference proceedings, textbooks)
2. No reference to medicines: title or abstract contained no reference to pharmaceuticals
3. No determinants of adherence: title or abstract contained no reference to determinants of adherence
4. No adherence data: full paper contained no empirical adherence data
5. Imprecise measure of adherence: does not measure medication adherence
6. No health psychology or economic model described: analysis of adherence did not include determinants associated with health psychology or economic theory
7. Post-hoc application of health psychology or economic theory: not a stated aim, objective or hypothesis of the study

4.4.5 Study selection

Eligibility assessment of title and abstract was performed independently in an unblinded standardised manner by two reviewer authors, using the inclusion criteria and exclusion criteria 1 to 3. If one reviewer coded a study as potentially eligible the full paper was retrieved. The full text of potentially eligible papers were retrieved and reviewed in the second stage of the screening process. Full papers were assessed using the inclusion and full list of exclusion criteria. Two reviewers were involved in this process, if there was disagreement, the papers were included and this was resolved at the data collection stage.

We did not apply any quality appraisal methodology because we included every paper that was eligible. PRISMA (9) recommends focusing on the risk of bias, rather than quality.

4.4.6 Data collection process

A data extraction form was developed, piloted on ten randomly selected included studies, and refined accordingly. Four researchers were involved in the data extraction. A single reviewer extracted data on study characteristics, participants and adherence measurement; then a second reviewer checked the extracted data and extracted data on the application of the theoretical model. Disagreements were resolved by discussion between the two reviewers (n=10); if no agreement could be reached a review author would decide (n=3). All data were extracted from the papers; no additional information was sought from authors.

4.4.7 Data items

Information was extracted from each study on: (1) study characteristics: aim and study design; (2) participant characteristics: disease, medicine, number, mean age, and gender; (3) adherence measure: measurement tool and method, unit of analysis, threshold for adherence definition and time-frame; (4) application of behavioural model: theory and components tested; (5) model measure: measurement tool and method, and number of participants included in the analysis; (6) results: results of study analysis, statistical techniques used, and model prediction. This list was amended after the pilot stage; medicines were added to participant characteristics; a separate field on the definition of adherence was removed as this was covered by the adherence measurement details; and, model prediction was added to results.

4.4.8 Risk of bias in individual studies

Bias refers to systematic deviations from the true underlying effect that may be attributable to poor study design, or data collection, analysis and interpretation procedures. To assess the validity of eligible studies a quality scoring system was developed. We hypothesised that prediction of medicines adherence may differ according to the quality of the measure of adherence, study design and sample size. Each aspect of each study was awarded a score from a 5-point scale:-

Adherence measure:-

5. Directly observed therapy **OR** electronic compilation of drug dosing histories (e.g. MEMS)
4. Medication measurement: therapeutic drug monitoring or counts of returned tablets
3. Prescription records
2. Self-report patient questionnaires and diaries
1. Assessment of patients' clinical responses and/or physiological marker or effect

Study design:-

5. RCT & prospective cohort
4. Panel Data
3. Retrospective cohort
2. Cross-sectional
1. Case report

Sample size [on a log scale]:-

5. 100,000-1,000,000+

4. 10,000-99,999
3. 1000, 9,999
2. 100-999
1. 10-99

A weighted quality score was calculated using the following algorithm:-

Weighting = (Adherence measure score*3) + (Study design score*2) + (Sample size score*1)

Quality scores were applied after the data collection process. The data (previously extracted by two reviewers) were sorted into the above categories and scored by a single reviewer. Studies were then ranked by quality (highest score = 1). Rank differences between the weighted and a simple aggregate score (adherence measure score + study design score + sample size score) were explored using descriptive statistics (absolute mean difference, number of studies occurring in both lists above a certain threshold).

Adherence measure was most highly weighted (*3), as the extent to which variability may be explained by behavioural models of adherence depends on the accuracy, precision and reliability of methods used to measure it. Scores were graded from objective (5 points) to subjective (1 point). Directly observed therapy was considered the most objective measure of adherence, although deliberate non-adherers may still feign taking medication, and, in it is often impractical. Electronic compilation of drug dosing histories scored equally as highly, representing a more practical measure in the outpatient setting, that is more reliable than patient self-report. Whilst there is a possibility that patients open & close electronic devices without taking anything out, pharmacokinetic studies show this is not a common phenomenon [ref]. Next we considered medication measurement, counting returned tablets over-estimates adherence, patients may discard what they have left before visiting their clinician (*"pill dumping"*), but gives an accurate medication possession ratio. Prescription refills indicate maximum adherence, so by definition will always over-estimate true adherence, however, they were considered more objective than self-report. Self-report questionnaires scored two. A review from 2004 comparing self-report with other methods found that of 86 studies identified, only 43% of the pairings of self-report and alternative measures were highly concordant 11. Whilst it is acknowledged that other measures are inaccurate, the likelihood is that self-report is most prone to bias. Finally clinical indicators were considered to be the most subjective, as there is so much variability both within and between patients, it becomes impossible to attribute non-adherence as the cause for any fluctuation in biomarker.

Study design was weighted (*2), second to adherence measure. Adherence may change over time, therefore longitudinal studies considered superior to cross-sectional studies. Finally, sample size was graded on a log scale. Further consideration could be given to the measure

of the theory and subsequent analysis; however given the breadth of this cross-discipline review, this was not implemented at this stage and would be more appropriate for analysis in peer-review publications that results from this review.

The assessment of bias described here was used to rank the quality of the evidence when in the data synthesis that followed.

4.4.9 Summary measures

The primary measure of adherence could not be predefined because of the heterogeneity in the outcome measures and statistical techniques used across the studies used to test theoretical models. Data extracted on methods and instruments used to measure adherence, and, psychological and behavioural outcomes, reported in this report, were scrutinised to ensure scales were fully understood to assess comparison. Significant predictors of adherence ($p<0.05$; $p<0.01$) were tabulated, but meta-analyses were not performed.

4.4.10 Synthesis of results

A narrative synthesis was undertaken as the studies were too diverse to be combined quantitatively 12. The framework for this synthesis was to develop a basic outline of predictors of adherence; tabulate the evidence by quality criteria; explore the relationship between studies (theories and model parameters tested); and, to develop a conceptual framework.

4.4.11 Risk of bias across studies

The review is restricted to studies published in peer-review journals. Risk of bias across these studies will be assessed by comparing studies that featured in other publication types, such as dissertations and book chapters, identified in the original search.

4.4.12 Additional analysis

Additional analysis of the final result will be conducted to explore heterogeneity and to report on sub groups. Sensitivity analysis will be used to explore the robustness of any quantitative results.

4.4.13 Study selection

The search of electronic databases identified 1746 health psychology papers and 534 economics papers after electronic de-duplication using RefWorks (ProQuest LLC 2010). Eleven additional health psychology papers and 18 health economics papers were identified by experts on the ABC team and by scrutiny of the reference lists of these papers.

Health psychology: 1757 publications were identified. 1208 were excluded following initial screen of title and abstract. 549 full-papers were sought, 482 (15 unobtainable) were excluded for the pre-defined exclusion criteria. Finally, 67 papers have been included in the review for their direct application of health psychology theory to explain adherence to medications.

Health economics: 552 publications were identified. 402 were excluded following initial screen of title and abstract. 150 full-papers were sought, 128 (2 unobtainable) were excluded for the pre-defined exclusion criteria. Finally, 22 papers have been included in the review for their direct application of economic theory to explain adherence to medications.

A total of 89 publications were included in the review. 17 potential papers were unobtainable.

See PRISMA flow diagram 9, Figures 2 and 3, for a full breakdown of study selection.

4.5 Results

4.5.1 Study characteristics

The study characteristics of all the studies included in the review are detailed in appendices 4.4 and 4.5.

Study design and participants

The majority of studies identified in the review were cross-sectional (n=64). Sample sizes ranged from 12 patients [168] to 199,179 individual prescription payment records[126]. Disease categories were broad, studies mainly reported patients with chronic diseases. Twenty-four studies focused on ART for the treatment of HIV. Other commonly cited conditions were related to hypertension (n=11), mental health (n=5), asthma (n=4), renal transplantation/disease (n=4), and diabetes (n=3). Eight studies considered multiple chronic diseases; these studies had larger sample sizes. Mean age of the patient population was always reported and ranged between 34.1 and 77.6 years. Gender was representative of the disease setting in most studies; one study of copayments on prescription data was 95% male; this can be explained by the 'veteran' sampling frame [138].

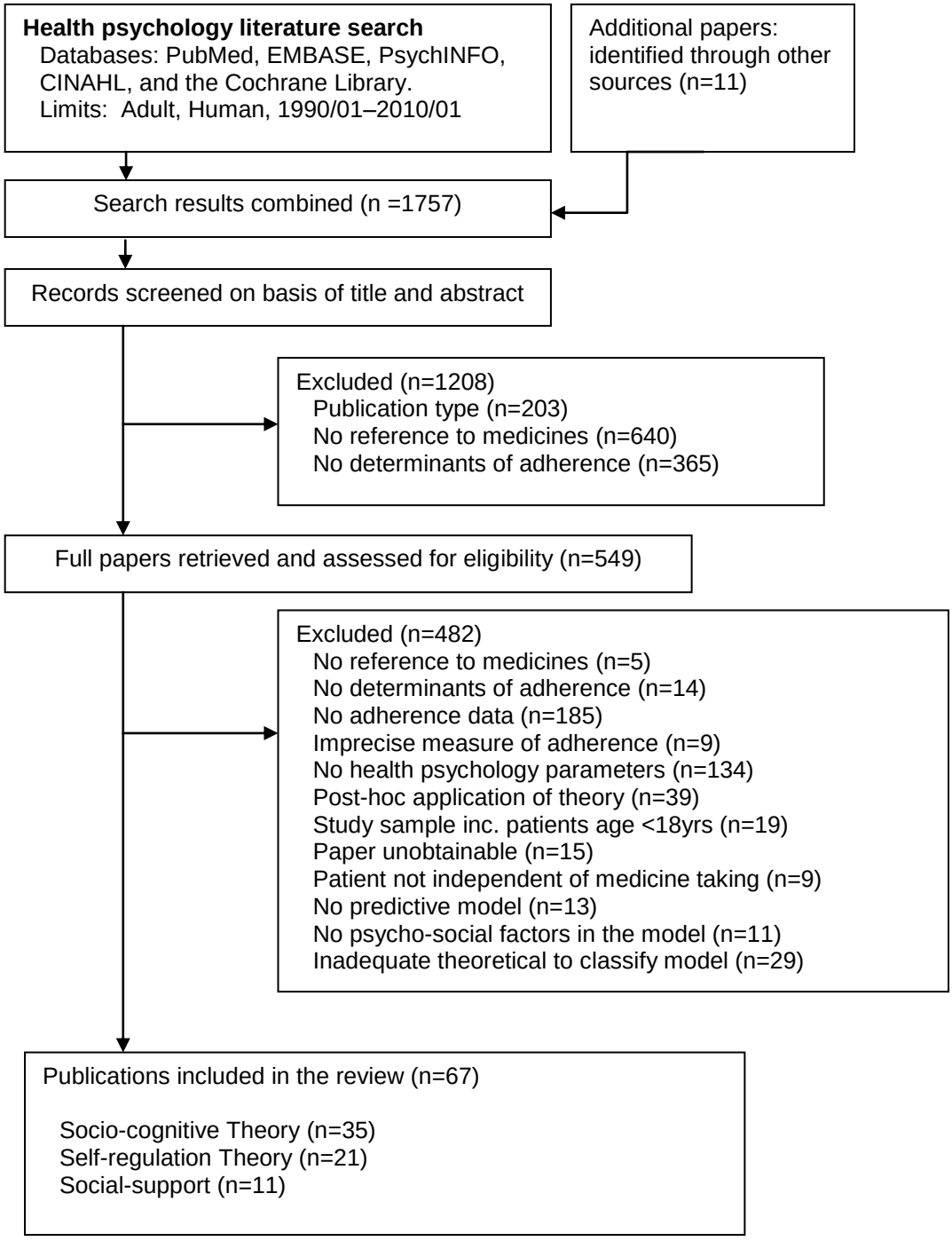

Figure 4.2: Flow diagram of health psychology study selection

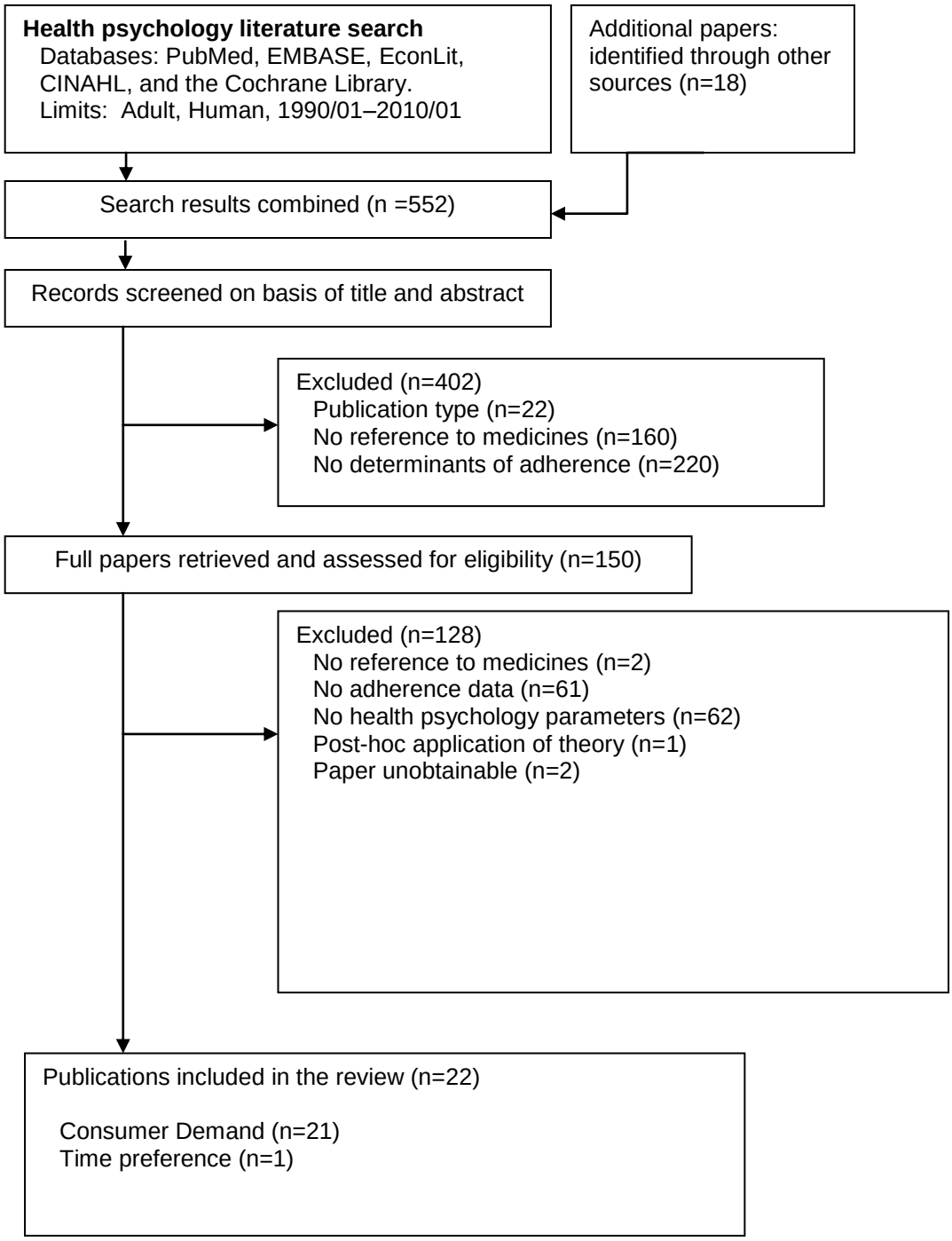

Figure 4.3: Flow diagram of behavioural economics study selection

Adherence measure

Figure 4.4 shows a frequency histogram of adherence measures. Over two-thirds of studies used self-report measures of adherence (n=57); these included interviews (n=12) and mainly questionnaires (n=45), often using validated or previously published instruments; such as:-

- Adult Adherence to Combination Therapy Questionnaire (AACTG) (n=7)
- Morisky Medication Adherence Scale (MMAS) (n=6)
- Medication Adherence Report Scale (MARS) (n=5)

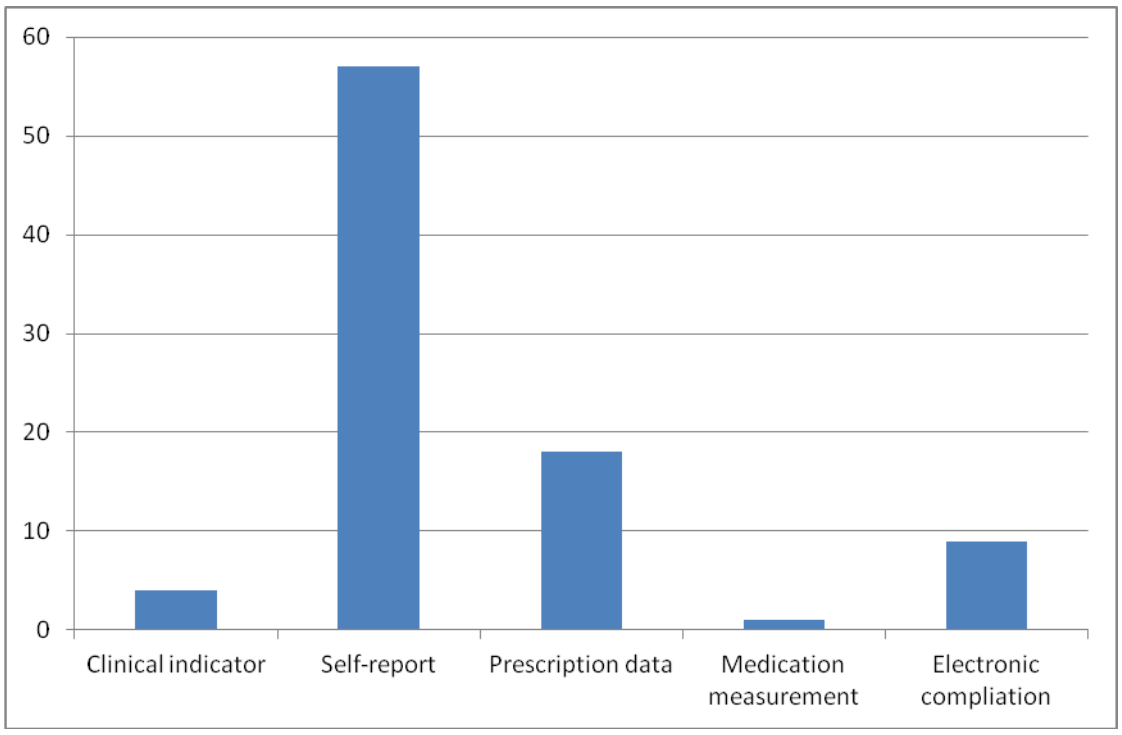

Figure 4.4: Frequency histogram of types of adherence measure (n= 89 studies)

Self-report measures were more popular in the health psychology literature (n=50/67). The most commonly used measure in economic studies was prescription record review, namely drug utilisation (15/22); these studies reported the longest time frame of adherence data; over as many as 1,095 days[124]. Studies of multiple medicines for a variety of conditions also used this measure most frequently: 20% of studies based on prescription methods considered adherence to multiple medicines.

Electronic monitoring was most commonly used in studies of ART (n=5). All the studies using MEMS (Medication Event Monitoring Systems) assessed psychological determinants (n=9), using longitudinal study design, the timeframe of these studies ranged from 1 week[78] to 15- months[47,113].

Adherence measurement, study design and sample size were associated, as shown in table 4.1. MEMS and DOT used longitudinal designs with small sample sizes, whereas prescription data automatically resulted in larger sample sizes, and self-report measures where used in small cross-sectional studies.

A number of studies reported using more than one type of measure and combining them, or reporting two independent scores [11, 14, 71, 102, 123]. Interestingly one such study [11], that used self-report and prescription record review, did not report the results of the latter, due to a poor response from community pharmacists, consequently all the analysis was conducted using a self-report measure.

Table 4.1: Studies categorised by adherence measurement, study design and sample size

Adherence measurement	Sample size – log scale categories (n)					
	10-99	100-999	1,000-99,999	10,000-99,999	100,000-1,000,000+	Total (no. studies)
MEMS or DOT	**3**	**6**				**9**
Longitudinal	*3*	*6*				*9*
Cross-sectional						
Medication measurement	**1**					**1**
Longitudinal	*1*					*1*
Prescription data	**1**	**4**	**6**	**5**	**2**	**18**
Longitudinal	*0*	*2*	*2*	*1*	*1*	*6*
Cross-sectional	*1*	*2*	*4*	*4*	*1*	*12*
Self-report	**6**	**48**	**3**			**57**
Longitudinal	*1*	*7*				*8*
Cross-sectional	*5*	*41*	*3*			*49*
Clinical indicator	**3**	**1**				**4**
Longitudinal		*1*				*1*
Cross-sectional	*3*					*3*
Total (no. studies)	**14**	**59**	**9**	**5**	**2**	**89**

Behavioural models

The studies identified in the behavioural economics literature (n=22) represented application of two theories, consumer demand and time preference. Twenty-one studies investigated the theory of consumer demand, studies often examined more than one aspect:-

- Price (n=14)
- Quantity (n=5)
- Substitution effects (n=3)
- Income (n=6)
- Budget constraints (n=2)
- Utility maximisation (n=1)

Four studies investigated the theory of time preference, they were all contained within the one paper[123], two aspects:-

- Health (n=2)
- Financial (n=2)

The majority of studies examined the influence of changes to prescription charges, such as copayments (n=13). Studies also investigated the impact of changes in income and expenditure on demand (n=4).

Components of consumer demand theory were mainly measured using electronic drug utilisation databases, specifically refill data. Questionnaires were also used, to assess affordability [budget constraints]. Time preferences were measured using hypothetical scenario questionnaires in an interview format; both health and financial time preferences were measured.

The studies reviewed from the health psychology literature (n=67), have been based primarily on socio-cognitive theory (n=35), self-regulation theory (n=21), and social support (n=11). Sociocognitive theory was applied using the health beliefs model (n=20), measuring items such as perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action, and health motivation; the theory of planned behaviour (n=5), measuring expected outcomes, attitudes, perceived behavioural control, normative beliefs, motivation to comply, behaviour intention, theory of reasoned action (n=2), protection-motivation theory (n=1), and the integrated model of behavioural prediction (n=1). Specific adherence socio-cognitive models were also identified, such as the Information-motivation-behavioural skills (IMB) model (n=3)

Self-regulation theory was applied in the context of the self-regulation model (n=16), self-determination theory (n=3) and social-action theory (n=2).

Social support was explored generally (n=5), using the transactional model of stress and coping (n=3) and in the context of family resiliency theory (n=1), social-problem solving (n=1), and generic coping alongside self-efficacy (n=1).

Health psychology studies used customised and previously validated questionnaires (e.g. version of the illness perceptions questionnaire [IPQ] (n=6); beliefs about medicines questionnaire [BMQ] (n=14), to measure cognitions. The majority of survey instruments used Likert scales to measure cognitions.

Table 4.2: Summary of studies with quality score ≥50% (n=36)

First author		Quality Assessment				Disease	Theory
		Adherence measure	Study design	Sample size	Weighted score / 30		
Gonzalez 2007	[47]	5	5	2	27	HIV	SRT
Weaver 2005	[113]	5	5	2	27	HIV	SS
Halkitis 2007	[52]	5	5	2	27	HIV	SS
Lynam 2009	[78]	5	5	2	27	HIV	SRT
Barclay 2007	[12]	5	5	2	27	HIV	SCT
Stilley 2004	[104]	5	5	2	27	Cholesterol	SCT
Schmitz 2005	[98]	5	5	1	26	Smoking cessation	SCT
Apter 2003	[5]	5	5	1	26	Asthma	SCT
Cohen 2004	[28]	5	5	1	26	Depression	SCT
Hsu 2006	[126]	3	5	5	24	Various chronic	CD
Brus 1999	[16]	4	5	1	23	Rheumatoid arthritis	SCT
Atella 2006	[118]	3	4	4	21	Hypertension	CD
Abraham 1999	[1]	2	5	2	18	Malaria	SCT
Gibson 2006	[124]	3	2	5	18	Hyperlipidaemia	CD
Cole 2006	[184]	3	3	3	18	CHF	CD
Balu 2009	[120]	3	3	3	18	Dyslipidaemia	CD
Gregoire 2002	[125]	2	5	2	18	Hypertension	CD
Johnson 2009	[63]	2	5	2	18	HIV	SS
Simoni 2006	[101]	2	5	2	18	HIV	SS
Williams 1998	[114]	2	5	2	18	Not stated	SRT
Lim 2004	[163]	2	5	2	18	Geriatric medicine	SCT
Farquharson 2004	[37]	2	5	2	18	Malaria	SCT
Fraser 2004	[43]	2	5	2	18	MS	SCT
Zeber 2007	[138]	3	2	4	17	Various	CD
Wang 2008	[136]	3	2	4	17	Depression	CD
Kephart 2007	[128]	3	2	4	17	Various chronic	CD
Thiebaud 2008	[135]	3	2	4	17	Various	CD
Bhosle 2007	[121]	3	3	2	17	Glaucoma	CD
Mishra 2005	[132]	3	3	2	17	Tuberculosis	CD
Turner 2007	[106]	2	5	1	17	MS	SCT
Rodin 2009	[133]	3	2	3	16	IHD & diabetes	CD
Ye 2007	[137]	3	2	3	16	IHD	CD
Jackson 2004	[127]	3	2	3	16	Various	CD
Zhang 2007	[139]	3	2	3	16	Hypertension	CD
George 2007	[45]	3	2	2	15	Heart failure	SCT
Chisholm 2007	[23]	3	2	2	15	Renal transplantation	SCT

4.5.2 Risk of bias within studies

Weighted quality scores for individual studies ranged from 8/30 to 27/30. The mean quality score was 15/30. Six studies shared the top rank, scoring highest on adherence measure (MEMS) and study design (prospective cohort). A summary of studies with quality Score ≥ 50% (n=36), including individual scores awarded for adherence measure, study design and sample size, are shown in table 4.2.

4.5.3 Results of individual studies

The results of the individual studies are detailed in data extraction sheets provided in appendices 4.3 (health psychology studies, key findings) and 4.5 (behavioural economic papers, model and results–data extraction).

4.5.4 Synthesis of results

Study designs, measures of adherence, and reported predictors varied markedly and were therefore too diverse to be combined quantitatively 12. We focused on describing the studies, their results and consolidating evidence from individual studies in a conceptual framework of patient behaviour.

A basic outline of a potential conceptual framework for the determinants of adherence was postulated (figure 4.5). This is based on health psychology models derived from social-cognitive theory, self-regulation theory, and social support; and, economic theories of consumer demand and time preference theory (figure 4.6); and can also accommodate individual models from within theories (figure 4.7).

4.5.5 Risk of bias across studies

Health psychology and behavioural models identified in the review of peer-review journals were consistent with those identified in other publication types, such as book chapters and dissertations. Non-English language studies were based on models derived from theories identified in the English language papers. Significant and non-significant model parameters were reported for most studies.

4.5.6 Additional analysis

Additional analysis of the agreed theoretical framework will be conducted in the future, using empirical and secondary data collected in other ABC study work packages.

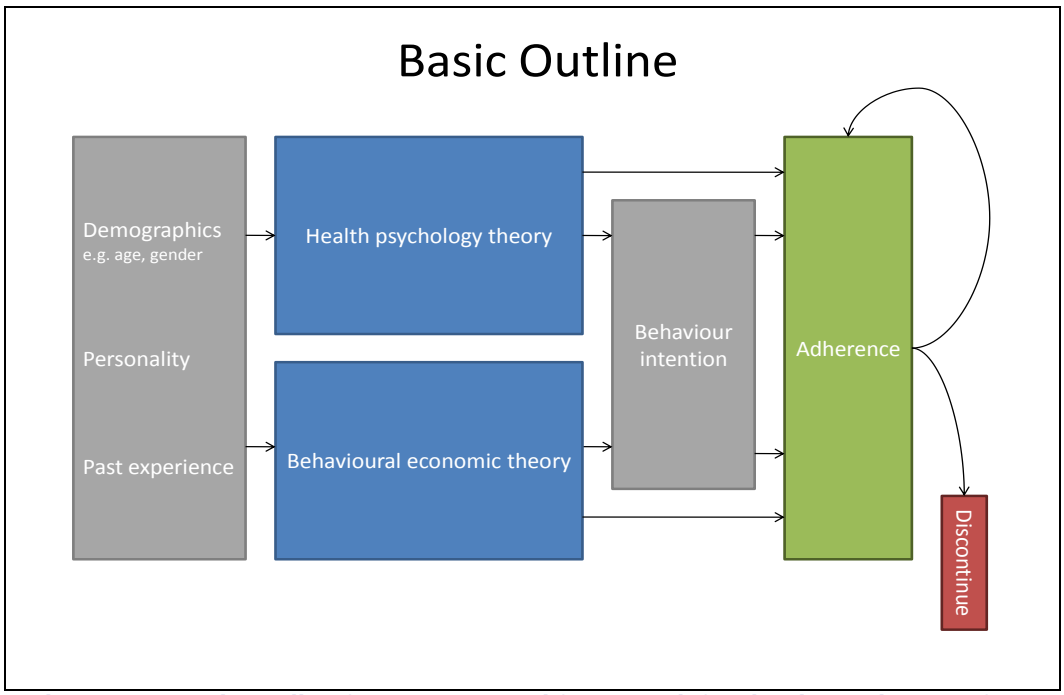

Figure 4.5: Basic outline for a conceptual framework for the determinants of non-adherence

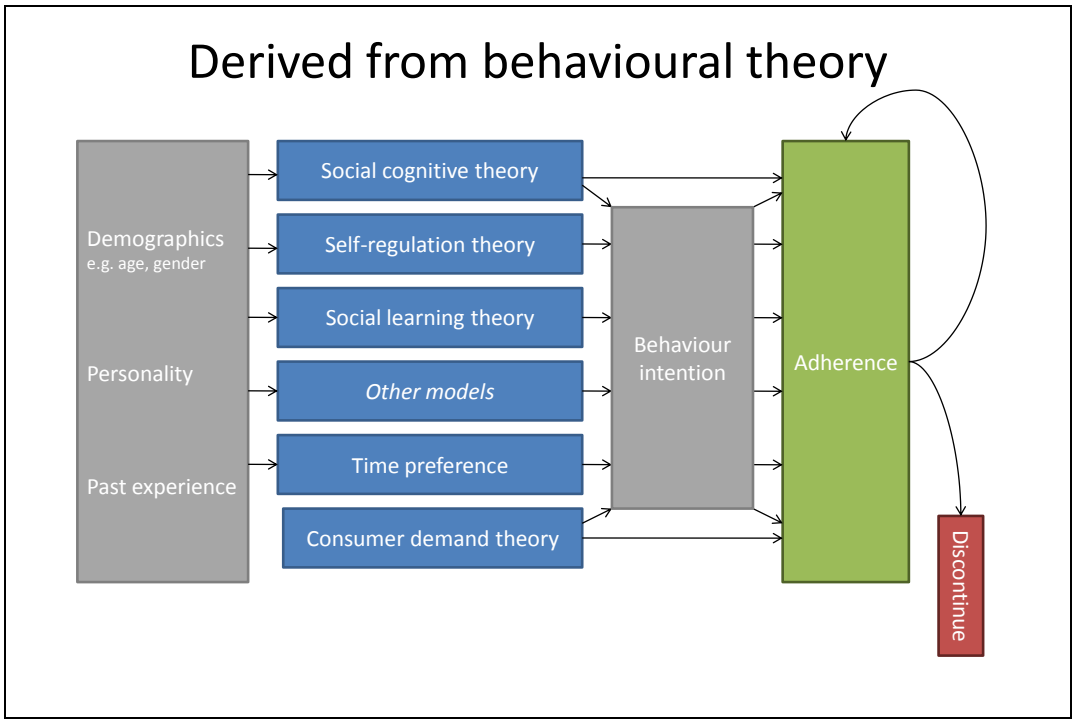

Figure 4.6: Explanation of how behavioural theory fits the basic outline

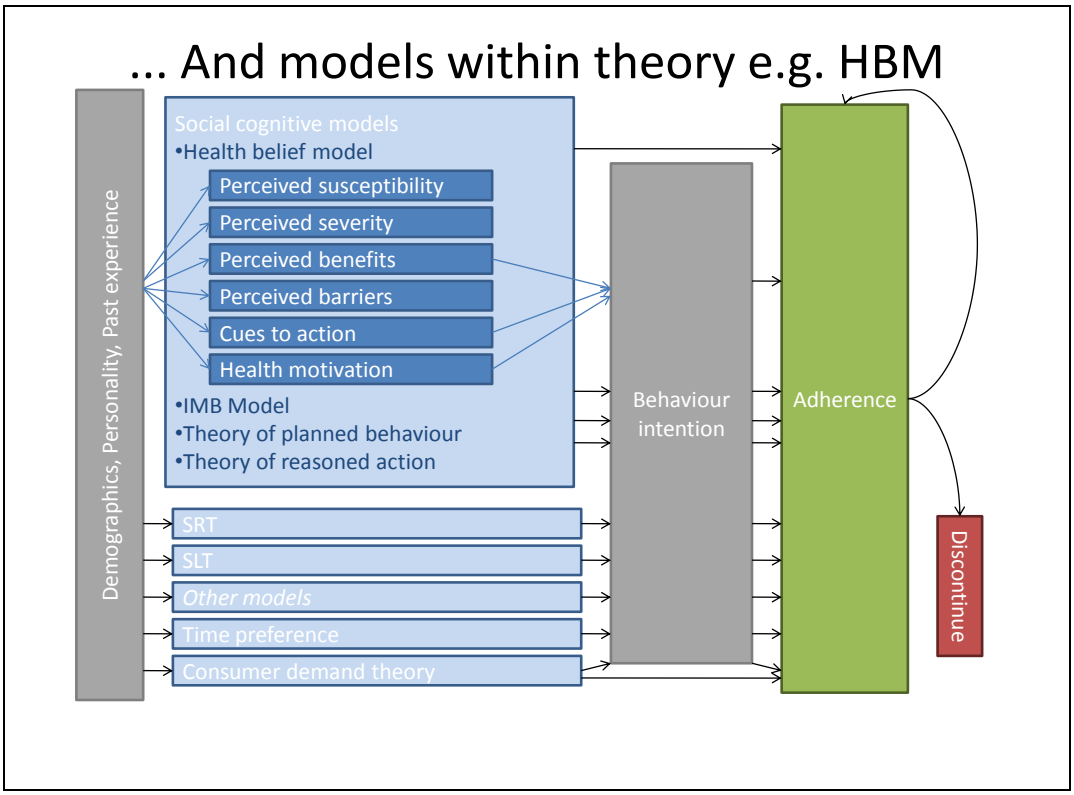

Figure 4.7: Example of how individual models within theory would fit the basic outline

4.6 Discussion

4.6.1 Summary of findings

It is important, when referring to non-adherence, to distinguish between unsatisfactory execution of a prescribed drug dosing regimen, and early, complete termination of dosing (short persistence). This distinction is fundamental, because failure to distinguish one from the other makes any assessment dependent upon the length of the study. Thus, a patient who doses correctly for 90 days and then discontinues altogether will be classified as 100% adherent if observed for 90 days, 50% adherent if observed for 180 days, and 25% adherent if observed for 360 days.

This distinction was unclear in the majority of studies. Most investigators classed patients dichotomously as being "adherent" or "non-adherent" according to some pre-specified (and arbitrary) threshold. Combined with the frequent reliance on self-reported adherence, this reduces the ability to assess the relative contribution of each of the behavioural models identified as determinants of the various forms of non-adherence, and represents an important limitation to the interpretation of the findings.

The literature review identified empirical evidence from health psychology and behaviour economic theory may contribute to our understanding of adherence. Parameters identified as determinants of adherence may help guide the development of interventions to improve adherence, and ultimately health outcome.

Adherence-related behavioural sciences provide a theoretical basis for the development of adherence enhancing interventions – the interventions target the determinants of non-adherence, and patient adherence is the resulting revealed behaviour. But, without valid measurement techniques, feedback as to the success of the intervention is limited. In order for the theoretical base suggested here, to be fully assessed it is necessary to bridge this gap with a dynamic model of adherence, figure 4.8.

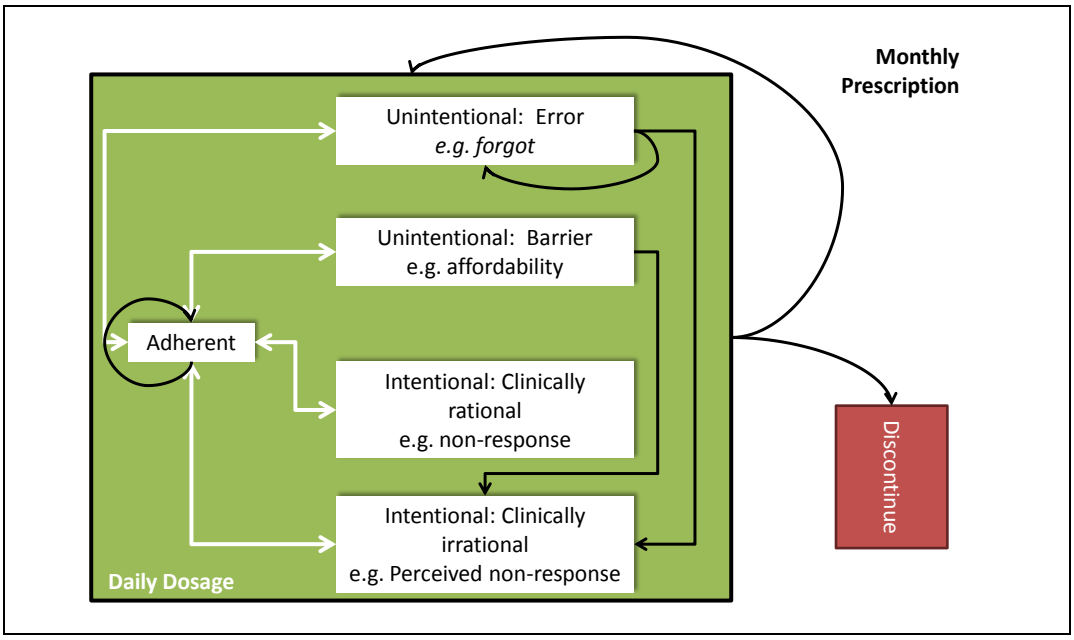

Figure 4.8: Dynamic model of (non)-adherence

This model enables two different time states to be assessed. Here, we suggest a 'daily' routine of adherence or states of non-adherence, and a monthly cycle of prescription refill or medication review. On a daily basis a patient can move between states of intentional or unintentional non-adherence. Unintentional non-adherence could be in error e.g. forgot, or due to a barrier, for example cost. Intentional non-adherence may be clinically rational (from the perspective of the prescriber) e.g. lack of efficacy, or irrational e.g. a perceived non-response. The transitional probabilities between states may be informed by the theoretical constructs of the conceptual framework – for example, a patient's perceived severity of their illness, as described by the health belief model, may explain their transition between an unintentional error (forgot) and their decision to adhere again. Models derived from the theories discussed here, may further contribute to our understanding of adherence if a dynamic approach to measurement of behaviour and the impact of interventions is adopted.

Economic theory, supported by empirical evidence, suggests that for a normal good, increased price of a good leads to reduced demand 13. Within the context of taking medicines, the costs associated with medicines can be complex. Depending upon the health system and an individual patient's insurance coverage, a patient may have access to free medicines, pay a fraction of full price such as a co-payment, or incur the total market price of the medicine. Prices of medicines are also subject to complex mechanisms, depending upon the presence, or not, of a generic preparation. Also, the same medicine may have different prices depending upon national, regional or local contracting or reimbursement arrangements. The effect of "cost-sharing" by patients is twofold: to produce revenue for the payer, and to reduce inappropriate

demand ("ex-poste moral hazard"). The full transaction price of medication may also include the cost of the time to purchase and use the health services that has been shown to be significant in some medical services.

From this evidence, we see that traditional models of consumer choice under a budget constraint do apply to medication taking behaviour in that increased prices cause decreased utilization. However, these models do not fully illustrate or explain medication-taking behaviour. For example, prescription medicines are free to 85% of the UK population, and yet adherence and persistence rates are no higher than in other countries.

According to consumer choice theory, one would also expect that financial incentives might encourage patients to adhere. This is supported by evidence which suggests that compensating individuals for the time, effort and cost involved with taking medicines is an effective measure to improve adherence 14. Financial incentives in the form of cash, vouchers, lottery tickets, or gifts are associated with improvements in the percentage of patients complying. Ten out of the 11 studies identified in the systematic review showed that some form of financial incentive promoted adherence better than any alternative.

Time preference refers to the extent to which decision makers (such as patients) are ready to trade-off between short-term costs and/or gains with long-term costs/gains that are associated with a particular course of action. Such decisions are a function of the value placed on future outcomes relative to immediate ones. The concept of time preference can be extended to understand peoples' medication adherence behaviour. The association between time preference and medication adherence, however, has not been investigated extensively, and has not been proven empirically. In assessing the decisions of working adults to accept or decline a free influenza vaccination offered at their workplace, Chapman[123] found very little relationship between scenario measures of time preferences and the acceptance of vaccine; or adherence to cholesterol-lowering medicines. Adherence to antihypertensive treatments was observed to correlate with time preference.

Health psychology models derived from social cognitive theory, self-regulation theory, and social support have been applied to studies of medicine adherence. Results point to the importance of self-efficacy as a core component; of relevance to social cognitive theory, given its conceptual relationship with perceived behavioural control (Theory of Planned Behaviour). Additionally, and perhaps more uniquely these findings point to the importance of the predictive utility of beliefs about medicines; a more recently explored aspect of self regulation theory. Distal predictors associated with personality are also suggested to be predictors, alongside other more distal variables, such as knowledge and global cognitive function (moderated by age). Past experience is also a significant predictor, which is often omitted from studies, and yet evidence has shown that past behaviour is a good predictor of future behaviour.

The conceptual model will be further developed on the basis of these studies and in consultation with experts in the field of adherence research.

4.6.2 Limitations

This review was restricted to studies published >=1990 and adult patients. Studies of adolescents were identified that investigated health psychology models, but there were excluded in keeping with the pre-defined protocol.

4.6.3 Implications and recommendations

Behavioural models based on both health psychology and economics have been applied to empirical studies of determinants of adherence to medicine.

Findings related to behavioural models drawn from the economic literature indicate that when access to medicines requires payments, patients' adherence to therapy follows the consumer demand theory, as if medicines were a normal good. However, the theory fails to explain all the variation in adherence, as lack of adherence, and premature discontinuation is highly prevalent in countries where health systems enable free access to medicines.

Findings related to models derived from social cognitive theory, self regulatory theory and social support also indicate that psychological factors can explain variance in medication adherence.

Distal and proximal parameters derived from behavioural theories have been shown to be significant predictors of adherence. The potential for these factors to be consolidated in a conceptual framework of patient behaviour has been demonstrated. This will provide a theoretical basis for the development and assessment of adherence-enhancing interventions. The interpretations of these findings are limited by unreliable measures of adherence. The dynamic properties of intentional and unintentional adherence warrant further investigation.

Future research is needed to test the effectiveness of adherence-enhancing interventions that are based on the theoretical models identified to have the greatest explanatory power of behaviour.

To our knowledge this is the first study to review both health economic and health psychology behavioural models of adherence.

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5 Exploring the current practices of adherence management by healthcare professionals and the pharmaceutical industry

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Survey of Pharmaceutical Company Initiatives to Improve Medication Adherence in Europe

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Survey of European Health Care Professional Educational Programs' Content on Managing Medication Adherence

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5.1 Summary

This chapter moves beyond a focus on patient factors to examine some of the broader influences operating on adherence. As illustrated by the World Health Organisation's five-dimension model of adherence,[1] patient-related variables represent only one aspect of a complex range of factors that interact to determine patients' adherence. This chapter focuses on healthcare team and health system factors, which have received relatively little attention in the literature to date. The roles of a variety of stakeholders are examined in order to elucidate a comprehensive account of activity for adherence at the levels of the healthcare team and health system. First, a survey is reported on the use of adherence-enhancing methods by the pharmaceutical industry. Two strands of research on healthcare professional factors are then presented; i.e., a) a survey of Schools of Medicine, Pharmacy and Nursing in 16 member states of the European Union regarding the methods of adherence management included in their curricula, and b) a survey of the beliefs, perceptions and behaviour of healthcare professionals in relation to assessing and improving patients' adherence to prescribed medication. Finally, we present a systematic review of existing national and international guidelines on the improvement of patient adherence in European and non-European countries.

5.2 Introduction

Literature in the field of medication adherence is dominated by research on patient factors, such as beliefs about the necessity of medication, memory difficulties, and concerns about the side-effects of medication. Although the role of the patient in adherence is clearly important, there are a number of other contributory factors that have received far less research attention.

One important stakeholder group in the field of adherence is the pharmaceutical industry. The pharmaceutical industry has the potential to support patients' adherence in a variety of ways, for instance through the simplification of dosing; provision of electronic dose-dispensing equipment; development of mobile technology; targeted designing of medication packaging; and production of objective measures of adherence behaviour. However, there exists no inventory of the methods used by this industry to promote patients' adherence to medication.

In order to gather information on methods used by the pharmaceutical industry in supporting patients' adherence, a survey was sent to 98 pharmaceutical companies across Europe. This information is needed not only to indicate current activity for adherence within the industry but also to signify opportunities for the development of the industry's role.

Healthcare professionals also have an important role to play in supporting patients with medication adherence. However, there is relatively little literature dealing with the training, beliefs or practices of healthcare professionals in this area.

Evidence from the USA has suggested that, despite the importance of training in enabling healthcare professionals to assess adherence and implement appropriate interventions to address non-adherence, few physicians receive formal training on adherence.[2] Little is known about the formal training on adherence received by European healthcare professionals. To address this gap in knowledge, a survey was sent to Schools of Medicine, Pharmacy and Nursing in 16 member states of the European Union, requesting information on current provision for adherence within the training of healthcare professionals.

There is a dearth of research on healthcare professionals' perceptions of non-adherence. While adherence to medication for long-term conditions has been estimated at only 50 per cent,[1] available evidence suggests that healthcare professionals underestimate the incidence of non-adherence in their patients.[3] This is consistent with research on optimistic bias,[4] which indicates that individuals perceive less risk for themselves relative to others. Further evidence is also needed on interventions used by healthcare professionals in the management of patients' adherence, as past research has been confined to interventions for cardiovascular patients[5] and the practices of physicians.[2] A survey of the perceptions, beliefs and practices of doctors, pharmacists and nurses with regard to patients' adherence to medication was conducted across 10 European countries to address this gap in the literature. The survey also assessed healthcare professionals' perceived barriers to implementing adherence-enhancing interventions and acquiring training on adherence management.

To gain a more complete understanding of healthcare professionals' practices in supporting patients with medication adherence, it was also necessary to examine their use of clinical guidelines on the promotion of patient adherence. In addition to gathering data on doctors', pharmacists' and nurses' use of clinical guidelines within the healthcare professionals' survey, a systematic review of existing national and international guidelines for the improvement of adherence was conducted. Guidelines within European and non-European countries were identified, retrieved and reviewed systematically to determine the support available for healthcare professionals' when addressing patients' non-adherence.

5.3 Objectives

- To identify and evaluate methods used by the pharmaceutical industry to promote patient adherence.
- To gather information on methods of adherence management included within the curricula of Schools of Medicine, Pharmacy and Nursing across 16 member states of the European Union.
- To determine the methods used by European healthcare professionals to manage non-adherence to prescribed medication in their patients.
- To determine perceived barriers to more frequent use of adherence-enhancing interventions by healthcare professionals.
- To systematically review national and international guidelines on enhancing patients' adherence in European and non-European countries.

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5.4 Survey of pharmaceutical company initiatives to improve medication adherence in Europe

Sabina De Geest, Kaat Siebens, Todd Ruppar, Fabienne Dobbels

5.4.1 Introduction

The pharmaceutical industry is one of the key stakeholders in medication adherence efforts. The industry seeks to maximize profit on the resources they invest in developing and marketing medications. Poor adherence leads to poor clinical outcomes, which affects the public perception of a medication's effectiveness and will lower refill rates due to patients' discontinuing treatment. Discontinuation of treatment leads to poorer health outcomes for the patient as well as lowered sales for the pharmaceutical industry. Thus, the industry has a vested interest in identifying and promoting methods to enhance adherence to medications. The type and extent of industry programs and efforts to improve medication adherence remain unknown, however, by the research, clinical, and policymaking communities. The current project aims to assess and describe the methods currently used by the pharmaceutical industry to promote patient medication adherence.

5.4.2 Objectives

To evaluate:

- whether pharmaceutical companies in Europe include medication adherence in their strategic plans.

- what general methods pharmaceutical companies identify as ways in which they support medication adherence-enhancing interventions.
- what specific interventions pharmaceutical companies report to be taking to improve patient adherence to prescribed medicines.

5.4.3 Method

5.4.3.1 Design

This project was a cross-sectional survey of pharmaceutical companies and their practices related to promoting adherence to medications. An internet-based survey tool was developed by experts in medication adherence from the ABC Project, with input from pharmaceutical industry consultants (appendix 5.1). The survey tool was reviewed by medication adherence experts for content validity, and pilot testing was completed. The survey was administered online using the web-based survey tool provided by Survey Monkey.

5.4.3.2 Setting

The targets of the current survey were the 40 full-member companies and 31 national associations of the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the 27 member companies of the European Generic Medicines Association (EGA).

5.4.3.3 Recruitment

The investigators contacted the president and the director general of EFPIA as well as the president and a member of the executive committee of the EGA to invite global offices of their companies and national associations to participate in the research.

All the global offices from the 40 full member companies and the 31 national associations from EFPIA and the 27 member companies of EGA received an email with background information about the ABC project and an invitation to participate in the research with a link to the online survey.

Four weeks after the first invitation all the companies and national associations received a reminder invitation by e-mail.

5.4.3.4 Analysis

Given the relatively low sample size, only descriptive statistics could be used: all data are described as absolute numbers, percentages, and median and range.

5.4.4. Results

Of the 40 companies and 31 national associations of EFPIA and the 27 companies of EGA that were invited to participate in the study, 9 companies filled in the on-line questionnaire.

Inclusion of medication adherence in the company's strategic plans.

Four (44%) of the nine companies indicated that medication adherence interventions are currently addressed in the company's strategic plan.

General methods to support medication adherence-enhancing interventions.

Four (44%) companies reported to provide initiatives to enhance medication adherence at a global level, four (44%) at a regional level (e.g., Europe, Asia-Pacific, etc.), seven (78%) at a national/country level and one (11%) company at a local (within country) level. Six companies (67%) indicated not having a dedicated division or staff addressing medication adherence within their company and three (33%) reported they had: one within the medical division, two within the marketing division and all three within research and development. Eight (89%) companies reported to have programs for adults and two (22%) for pediatric patients. Table 5.1 gives an overview of the reported programs by the companies to improve patients' medication adherence for the specific types of medication.

Table 5.1: Company programs per type of mediation

Company programs	Number of companies
All conditions/products	2 (22%)
Allergy/Cold/ENT	0 (0%)
Analgesics	1 (11%)
Antimicrobials/Anti-infectives	2 (22%)
Asthma/Pulmonary	3 (33%)
Cardiovascular	4 (44%)
Dermatologic	0 (0%)
Endocrine/Metabolic conditions	3 (33%)
Gastrointestinal	1 (11%)
Genitourinary	1 (11%)
Hematology/Oncology	1 (11%)
Immunologics/Immunosuppressives	1 (11%)
Neurologic	1 (11%)
Nutrition/Electrolytes	0 (0%)
Obstetrics/Gynecology	0 (0%)
Ophthalmic agents	1 (11%)
Psychiatric	1 (11%)
Rheumatologic	1 (11%)
Other	0 (0%)

Seven (78%) of the responding companies reported developing or providing interventions to improve medication adherence for patients, seven (78%) for healthcare professionals and one (11%) company for community-based intervention strategies (e.g. public health, population-based initiatives).

Interventions to improve patient adherence to prescribed medicines.

Table 5.2 gives an overview of the interventions currently being used within the companies to promote patient adherence.

Five (56%) out of the nine responding companies described the development of health care professional-focused reading material on how to address medication adherence as currently used methods targeting healthcare professionals to promote patient adherence. One (11%) company reported the development of videos/DVDs to train healthcare professionals, two (22%) reported the development of training sessions or workshops for health care professionals and finally two (22%) described drug-specific instructions for health care professionals to use when counseling patients who have missed doses as currently used methods targeting healthcare professionals to promote patient adherence. Finally, five (56%) companies reported to have a new medication adherence initiative planned over the next 12 months.

Table 5.2: Company interventions for patients and for family members or other caregivers

	For patients	For family members/caregivers
Development of written materials promoting medication knowledge and medication adherence	5/9 (56%)	5/9 (56%)
Development of videos/DVDs to promote medication adherence among patients	3/9 (33%)	1/9 (11%)
Publication of drug-specific instructions for patients about what to do if a dose is missed	2/9 (22%)	1/9 (11%)
Development of less complex medication regimens with fewer daily doses	3/9 (33%)	0/9 (0%)
Development of combination drugs to improve medication adherence	2/9 (22%)	0/9 (0%)
Development of patient-friendly drug delivery systems	4/9 (44%)	0/9 (0%)
Establishment of patient assistance programs to improve accessibility to medication for patients with financial need	3/9 (33%)	2/9 (22%)
Use of adherence-enhancing packaging methods	2/9 (22%)	0/9 (0%)
Distribution of reminder systems, pill organizers, etc.	4/9 (44%)	1/9 (11%)
Providing telephone adherence support to patients	4/9 (44%)	1/9 (11%)
Providing text message (SMS) reminders	4/9 (44%)	1/9 (11%)
Providing internet-based interventions	3/9 (33%)	0/9 (0%)
Interventions targeting individuals with limited financial resources	2/9 (22%)	0/9 (0%)
Interventions targeting patients with low literacy	0/9 (0%)	0/9 (0%)
Interventions targeting racial or ethnic minorities	1/9 (11%)	0/9 (0%)
Interventions targeting adolescents	0/9 (0%)	0/9 (0%)

Interventions targeting older adults/elderly	0/9 (0%)	0/9 (0%)
Other (please specify in the box below)	1/9 (11%)	0/9 (0%)

5.4.5 Discussion

5.4.5.1 Main findings and conclusions

As postulated in the design of the survey, at least some pharmaceutical companies consider themselves as stakeholders in the process of therapy adherence or consider it an important factor in the process of medication development and marketing, given the reported efforts in this field.

Striking is, however, the very low response rate: only nine companies responded to the invitation to participate. This might reflect a language problem, in that the questionnaire was only drafted in English. This is unlikely, as managers of multinational companies in general do speak and read English. Another possibility is that the survey invitations were not received by the appropriate person within many of the pharmaceutical companies. The urgency grade attributed to this project for those people was not set at the highest level, reflecting either a very busy schedule or a lack of interest in or specific knowledge of the subject. It is a fact that within companies of this magnitude it is very hard to find the person that is placed best to fill in surveys like the present one. Also, within medical companies politics come into play and confidentiality is a major factor. The latter issue will be challenging to resolve.

Only four (44%) of the nine companies indicated that medication adherence interventions were currently addressed in the strategic plan of the company. If this (together with the previously mentioned situations in staffing, with only one company out of three reporting to employ a staff member dedicated to therapy adherence) reflects the overall situation in the field (taking the low response rate out of the equation), this calls for more campaigns towards awareness and efforts in the field of therapy adherence within the pharmaceutical companies.

5.4.5.2 Strengths and limitations

To our knowledge this survey is the first of its kind, in that no prior evaluation of the practice of European pharmaceutical companies regarding medication adherence has been performed.

The most important drawback of the current survey is its extremely low response rate. Conceivably this creates a bias, in that companies that are more interested in this specific matter might be more inclined to respond. As a consequence the survey does not allow for firm conclusions. One of the possible causes for the lack of response might be the fact that inviting the companies through

EFPIA and EGA was not the most appropriate way to recruit. It might be that invitations were not send out to the people within the company who are informed to fill in the questionnaire.

5.4.5.3 Implications and recommendations

As a result of the poor response, firm conclusions cannot be drawn from this survey. Future efforts may benefit from using different methods to increase involvement of pharmaceutical companies in adherence initiatives. Political intervention might be required to get optimal involvement of the companies: making both reporting and development of adherence intervention programs mandatory might increase efforts on the side of the pharmaceutical industry. As an alternative an internet search could be performed, although this does not avoid the issue of confidentiality.

Future work addressing adherence should involve pharmaceutical companies or pharma trade associations (such as EFPIA and EGA) as partners and stakeholders. Such cooperation will improve the sharing of useful information and ensure that all involved are a part of any proposed solution.

5.5 Survey of European healthcare professional educational programs' content on managing medication adherence

Sabina De Geest, Kaat Siebens, Todd Ruppar, Fabienne Dobbels

5.5.1 Introduction

Non-adherence to medication is a global issue of major public health concern.[1] This problem is especially relevant to European Union countries, where access to healthcare services is good and their utilization is high. In such circumstances, no further improvement in the effectiveness of therapeutic and prophylactic medication can be realized without addressing patient non-adherence.

Given the high prevalence of medication non-adherence and its detrimental impact on clinical and economical outcomes adequate medication management by health professionals is key to guarantee optimal patient adherence. This implies that professionals have the skills to support patients in the process to take medication as prescribed both at initiation of treatment and in the long term after the treatment onset to avoid premature discontinuation of medication.[2]

The objective of management of adherence is to achieve the best use by patients of appropriately prescribed medicines in order to maximize the potential for benefit and minimize the risk of harm. This objective necessitates professionals who are prepared to support patients in this medication taking process. Ideally education and skills training on assessing the extent of non-adherence, its risk factors and evidence-based interventions is embedded already in the curricula of medical, pharmacy and nursing schools as these are the disciplines most closely involved in medication

management. It is however currently unknown to what extent these curricula contain training on these topics.

The current study aims to shine a light on the methods currently used by educational programs in medicine, pharmacy and nursing in 16 European countries in an attempt to meet the WHO's core competencies for preparing health care professionals to better address and manage patients' medication adherence.

5.5.2 Objectives

To evaluate:

- whether European high schools or universities of medicine, pharmacy, and nursing include medication adherence as a defined topic in their curricula.
- what content is provided about medication adherence in health care professional training programs.
- what specific methods European schools of medicine, pharmacy, and nursing use to educate future health care providers to address and improve patient adherence to prescribed medicines.

5.5.3 Method

5.5.3.1 Design

This cross-sectional descriptive study used an English-language self-report questionnaire designed by the researchers to collect data necessary to address the study objectives (appendix A). Items were developed collaboratively in an iterative process by members of the ABC Project team, who are experts in medication adherence. It was administered online using the web-based survey tool provided by SurveyMonkey.com

5.5.3.2 Setting

This study surveyed master and bachelor level schools of medicine, pharmacy and nursing in the 16 European nations covered by the ABC Project (Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, the Netherlands, Poland, Portugal, Spain, Switzerland, and the United Kingdom). The lists of schools were provided by the ABC partners in each country. Additionally, an internet search was executed to find more contact details of eligible schools. Medicine, pharmacy and nursing were chosen as these disciplines are most frequently involved in medication management.

5.5.3.3 Recruitment

Up to five schools of each type per country were selected for the survey (i.e. five nursing schools, five medical schools and five pharmacy schools). In countries with more than five of one of these types of schools, five schools from that country were chosen at random, using the formula: total number of schools/5=X and picking every {X}th school from a list of all the schools ordered alphabetically. In schools providing more than one education (e.g. nursing and medical school), a survey was sent to the program director of each school separately.

The head of the school or faculty was first contacted by phone by one of the researchers to explain the purpose of the survey and to obtain the contact information of the program director or the person most closely involved in developing the curriculum. Once the requested contact information was obtained, an e-mail with a personalized invitation letter, written information about the survey and a link to the electronic survey was sent to the respective persons.

5.5.3.4 Analysis

Given the relatively low sample size, only descriptive statistics could be used: all data are described as absolute numbers, percentages, and median and range.

5.5.4. Results

Invitations were sent to a total of 201 schools of which 75 schools of medicine, 61 schools of pharmacy and 65 schools of nursing in the 16 European nations covered by the ABC project. Of those, 22 respondents provided data for 24 schools, resulting in a response rate of 12%, 7 medicine, 9 pharmacy and 8 nursing training programs. Table 5.3 gives an overview of the response rate per country and school type. Twenty-three schools were based in a university and one in a vocational or technical school.

Implementation and content of medication adherence as a defined topic in the core curricula.
Twenty-one percent of the schools (n=5) indicated that ***'how to assess medication adherence'*** was not addressed in their school's curriculum. Of the respondents reporting that their curriculum contained specific content on how to asses medication adherence 71% (n=17) reported content via didactic/classroom/lecture training, 46% (n=11) via 'clinical/practicum/hands-on skills training and 33% (n=8) via case-studies.

Twenty-five percent of the respondents (n=6) reported their school's curriculum did not address content on ***'how to improve or promote medication adherence'***. Of the other schools 71% (n=17) reported that the curriculum contained specific content on how to improve or promote medication adherence via didactic/classroom/lecture training, 38% (n=9) via 'clinical/practicum/hands-on skills training and 25% (n=6) via case-studies.

Table 5.3: Response rate per country and school type

	Schools of Medicine		Schools of Pharmac		Schools of Nursing	
	Invited	Response	Invite	Response	Invite	Response
Austria	3	1 (33%)	3	1 (33%)	5	0 (0%)
Belgium	5	0 (0%)	5	2 (40%)	5	1 (20%)
Czech Republic	5	0 (0%)	1	1 (100%)	4	1 (25%)
Denmark	3	1 (33%)	1	0 (0%)	5	1 (20%)
Finland	5	0 (0%)	3	1 (33%)	5	0 (0%)
France	5	0 (0%)	5	0 (0%)	5	0 (0%)
Germany	5	1 (20%)	5	1 (20%)	4	1 (25%)
Greece	5	0 (0%)	3	0 (0%)	1	0 (0%)
Hungary	4	0 (0%)	3	0 (0%)	5	1 (20%)
Italy	5	0 (0%)	5	0 (0%)	2	1 (50%)
Netherlands	5	2 (40%)	2	2 (100%)	2	0 (0%)
Poland	5	0 (0%)	5	0 (0%)	5	0 (0%)
Portugal	5	0 (0%)	5	1 (20%)	2	1 (50%)
Spain	5	0 (0%)	5	0 (0%)	5	0 (0%)
Switzerland	5	1 (20%)	5	0 (0%)	5	1 (20%)
UK	5	1 (20%)	5	0 (0%)	5	0 (0%)
Total	75	7 (9%)	61	9 (15%)	65	8 (12%)

Respondents (n=18) reported a minimum of zero and a maximum of 56 contact hours of **'didactic (classroom) training or instruction for students regarding the 'assessment and management of medication adherence'** with a median of three contact hours training. When looking at the reported hours for the different types of schools, the schools of medicine (n=4) reported a minimum of zero and a maximum of ten and a median of two hours of training, the schools of pharmacy (n=6) reported a minimum of zero, a maximum of 15 and a median of 2 hours of training and the schools of nursing (n=6) reported a minimum of zero, a maximum of 56 and a median of 9.5 hours.

Respondents (n=15) reported a minimum of zero and a maximum of 20 contact hours of ***clinical (practicum/hands-on) or instruction*** for students regarding the ***'assessment and management of medication adherence'*** with a median of two hours, with one outlier reporting 300 hours of training. For the different types of schools this showed a minimum of zero, a maximum of four and a median of zero hours for the schools of medicine (n=3), a minimum of 2, a maximum of 20 and a median of 8 hours for the schools of pharmacy (n=5) and a minimum of zero, a maximum of four and a median of zero hours for the schools of nursing (n=5).

The majority of the schools (83%, n=20) reported that the recommended adherence training content is for ***patient***, 50% (n=12) for ***family/caregivers*** and 27% (n=6) for ***community-based intervention strategies (e.g. public health, population based initiatives)***.

Specific methods used in the education to address and improve patient adherence.

The following table gives an overview of the different methods institutions recommend to students to promote patient adherence to prescribed medication regimens targeting patients.

Table 5.4: Interventions targeting patients

	Interventions for patients			
	Total number of schools	**Schools of Medicine**	**Schools of Pharmacy**	**Schools of Nursing**
Face-to-face education	15/24 (63%)	5/7 (71%)	6/9 (67%)	6/8 (75%)
Printed educational materials	14/24 (58%)	3/7 (43%)	6/9 (67%)	5/8 (63%)
Goal-setting	7/24 ((29%)	1/7 (14%)	3/9 (33%)	3/8 (38%)
Feedback	9/24 (38%)	3/7 (43%)	3/9 (33%)	3/8 (38%)
Prescription of combination drugs to improve medication adherence	9/24 (38%)	3/7 (43%)	3/9 (33%)	3/8 (38%)
Prescription of less complex medication regimens with fewer daily doses	12/24 (50%)	5/7 (71%)	4/9 (44%)	3/8 (38%)
Motivational interviewing	9/24 (38%)	3/7 (43%)	3/9 (33%)	3/8 (38%)
Use of reminder systems, pill organizers, etc.	15/24 (63%)	3/7 (43%)	6/9 (67%)	6/8 (75%)
Targeting interventions to individuals with limited financial resources	2/24 (8%)	1/7 (14%)	0/9 (0%)	1/8 (13%)
Targeting interventions to patients with low literacy	5/24 (21%)	1/7 (14%)	1/9 (11%)	3/8 (38%)
Targeting interventions to racial or ethnic minorities	4/24 (17%)	1/7 (14%)	1/9 (11%)	2/8 (25%)
Targeting interventions to adolescents	5/24 (21%)	1/7 (14%)	1/9 (11%)	3/8 (38%)

Targeting interventions to older adults/elderly	14/24 (58%)	3/7 (43%)	5/9 (56%)	6/8 (75%)
Other (please specify in the box below)	0/24 (0%)	0/7 (0%)	0/9 (0%)	0/8 (0%)

Table 5.5 gives an overview of the different methods institutions recommend to students to promote patient adherence to prescribed medication regimens for family members or other caregivers.

Table 5.5: Interventions targeting family members or caregivers

	Interventions for family members or caregivers			
	Total number	**Medicine**	**Pharmacy**	**Nursing**
Face-to-face education	9/24 (38%)	4/7 (57%)	1/9 (11%)	4/8 (50%)
Printed educational materials	6/24 (25%)	2/7 (29%)	2/9 (22%)	2/8 (25%)
Goal-setting	2/24 (8%)	0/7 (0%)	1/9 (11%)	1/8 (13%)
Feedback	3/24 (13%)	2/7 (29%)	0/9 (0%)	1/8 (13%)
Prescription of combination drugs to improve medication adherence	4/24 (17%)	2/7 (29%)	1/9 (11%)	1/8 (13%)
Prescription of less complex medication regimens with fewer daily doses	4/24 (17%)	3/7 (43%)	1/9 (11%)	0/8 (0%)
Motivational interviewing	2/24(8%)	1/7 (14%)	0/9 (0%)	1/8 (13%)
Use of reminder systems, pill organizers, etc.	7/24 (29%)	2/7 (29%)	2/9 (22%)	3/8 (38%)
Targeting interventions to individuals with limited financial resources	2/24 (8%)	0/7 (0%)	1/9 (11%)	1/8 (13%)
Targeting interventions to patients with low literacy	2/24 (8%)	0/7 (0%)	0/9 (0%)	2/8 (25%)
Targeting interventions to racial or ethnic minorities	1/24 (4%)	0/7 (0%)	0/9 (0%)	1/8 (13%)
Targeting interventions to adolescents	4/24 (17%)	1/7 (14%)	1/9 (11%)	2/8 (25%)
Targeting interventions	7/24 (29%)	1/7 (14%)	2/9 (22%)	4/8 (50%)

to older adults/elderly				
Other (please specify in the box below)	0/24 (0%)	0/7 (0%)	0/9 (0%)	0/8 (0%)

Ten of the responding schools (42%) indicated the adherence education is offered at Bachelor level and 11 respondents (46%) at Master level. Two institutions indicated planning to start new medication adherence training initiatives over the next 12 months. One school of medicine indicated medication adherence training would be started as part of a governmental project. One school of pharmacy is planning to include the principles of motivational interviewing in the curriculum.

5.5.5 Discussion

5.5.5.1 Main findings and conclusions

The most striking finding of the current survey is the very low response rate with only one out of ten schools responding to the invitation to participate. This might reflect a language problem, in that the questionnaire was only drafted in English, or a lack of interest in the subject. It is also possible that the program directors contacted are not fully aware on the curricula's content, making it too time consuming for them, even if we kept the questionnaire deliberately short. This issue needs to be addressed further. Conceivably translation into the respective native languages and direct contact through an interview, either by telephone or in person with the person responsible for the curriculum, or specific courses within the curriculum might give a better overview of the current situation, but would be very intense. Given this low response rate our results need to be interpreted with caution.
Our survey nevertheless provides some food for thought as one out of five institutions reported not having specific content on how to assess medication adherence in their curriculum and 25% of the institutions even reported no specific content on how to improve or promote medication adherence.
Moreover the reported number of contact hours of classroom training and clinical training vary considerably for the different schools, with a median of three contact hours. Teaching seems to be the most utilized form of educating medication adherence.

Although we don't know how representative this is for the whole of Europe, the low median teaching time is of concern, given the complexity of the problem of medication non-adherence. One can question if three hours is sufficient to fully understand that medication non-adherence is a very prevalent problem with serious economic and clinical consequences, that risk factors are multifold and highly individually determined, that interventions that are effective are typically complex necessitating strategies tailored to the individual risk factors, and that such interventions must not only address the patient but also all levels of the health care system and be embedded in a chronic care perspective. In addition, even if this content is covered in the curricula the translation of factual knowledge into hands-on effective adherence management in clinical reality is questionable if no skills training is organized. Indeed, professionals need extensive training not only on how to assess

medication adherence but also on implementing evidence-based interventions to assure treatment initiation and continuation.

When looking at the interventions to promote adherence on a patient level, face-to-face education, the use of reminder systems, pill organizers and targeting interventions to older adults/elderly are most frequently reported. Comparable results can be seen for the interventions for family members and caregivers. The results demonstrate clearly that classroom training is again the most utilized form of educating medication adherence. Our results show that professionals seem to predominantly receive information/training on educational strategies, despite evidence clearly showing that education is a prerequisite but not an effective strategy to remediate adherence problems.[3] This is also in line with recent findings showing that professionals (e.g. nurses) heavily rely on educational, rather than behavioral strategies to tackle non-adherence in their clinical practice.[4 5]

Given that nurses, physicians and pharmacists receive training through advanced skills-labs and training in the field on various themes (resuscitation, EKG, venipuncture, etc.) it is surprising that no similar skills-labs exists on adherence management. This calls for European wide policy guidance on curricula reform, as a first step in guaranteeing that professionals are adequately prepared to deal with the complex problem of non-adherence.

5.5.5.2 Strengths and limitations

The major strength of the present work is the fact that it is a first-of-its-kind investigation and that its scope is Europe-wide. We are not aware of any other project with this vast coverage of the issue of adherence to medication.

The most important drawback of the current survey is its extremely low response rate, with even a complete absence of response in some countries. Yet, our limited findings suggest that current education and training about adherence management is sub-optimal. These insights might create a window of opportunity to reform core curricula in order to prepare professionals better in adherence support.

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5.6 Survey of European healthcare professional beliefs and behaviour regarding patient medication adherence

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5.6.1 Introduction

Systematic reviews conducted by Haynes and colleagues[1,] and other reviews show that interventions designed to improve adherence for chronic health problems, such as patient education, psychological therapy, simplified dosing and family intervention, tend to be complex in nature and low in effectiveness. However, the effectiveness of adherence-enhancing interventions needs to be examined in a broader context which encompasses the role of healthcare professionals. Healthcare professionals have an important role to play in providing support to patients in order to ensure that if patients agree to take medicines, they are used in a safe, effective, and cost-effective way. However, evidence suggests that healthcare professionals may not be fulfilling this role, as they tend to underestimate the incidence of non-adherence in their patients.[2] This is consistent with the literature on optimistic bias, which suggests that individuals perceive themselves to face less risk than other people.[3] It is possible that this phenomenon extends to healthcare professionals' perceptions of the behaviour of their patients. Research has also indicated that few physicians receive formal training in patient adherence, and that the assessment of patient adherence and the use of adherence-enhancing interventions is significantly greater among those who do receive formal training in this field.[4] Improving the skills of healthcare professionals in properly assessing the risk of non-adherence in patients and delivering interventions aimed at reducing non-adherence, may therefore lead to more effective support for patients taking prescribed medicines.

Research has examined the role of healthcare professionals in patients' adherence, although this has focused predominantly on physicians' communication and characteristics.[5 6] Despite evidence

from this research suggesting that healthcare professionals can significantly affect patients' adherence to medication, the majority of literature in the field has addressed patient factors, such as illness and treatment beliefs,[7 8] and memory difficulties,[9] while the beliefs, perceptions and practices of healthcare professionals have received relatively little attention. The challenges faced by healthcare professionals in addressing patients' non-adherence have also been under-researched. In order to gain a more complete understanding of non-adherence and address the gap in the current knowledge, this cross-sectional study assessed the perceptions, beliefs and behaviours of healthcare professionals - doctors, nurses and pharmacists – in 10 European countries with regard to patients' adherence to prescribed medication. Online surveys were used to gather data on healthcare professionals' perceptions of the extent of non-adherence to medication, beliefs about adherence to medicines, use and perceived effectiveness of interventions to manage non-adherence in their patients, perceived barriers to the use of adherence management interventions, and training in medication adherence.

The main objectives of the study were (1) to determine the perceptions of doctors, nurses and pharmacists of the extent of non-adherence in their nations and, in particular, their own patients; (2) to identify methods used by doctors, nurses and pharmacists in assessing patients' non-adherence to medication; (3) to determine the methods used by healthcare professionals to enhance patients' adherence, and the perceived effectiveness of these methods; (4) to ascertain the barriers faced by healthcare professionals in the use of adherence-management interventions, and (5) to explore differences between nations and professional groups in each of the aforementioned areas.

5.6.2 Methods

5.6.2.1 Participants

Between July 2011 and April 2012, cross-sectional data was collected in an online anonymous questionnaire survey of doctors, pharmacists and nurses working in primary care and community settings in ten European countries. Data was collected in Austria, Belgium, England, France, Germany, Hungary, The Netherlands, Poland, Portugal, and Switzerland. Healthcare professionals who satisfied the following criteria were eligible for inclusion in the survey:

a. They were currently employed as medical doctors, nurses or pharmacists
b. They work mainly with adults
c. They work mainly in the community or primary care
d. They work either in a private or public health care system (or both)
e. They are qualified and registered to practice
f. They consent to take part in the survey.

Healthcare professionals were not eligible to participate in the survey if:

a. They are student doctors, nurses or pharmacists
b. They work only in paediatrics (i.e. do not work with adult patients at all)
c. They work mainly in secondary care

d. Lack of consent from the healthcare professional or his/her decision to quit the study at any stage and for any reason.

The sample size calculation was based on the estimation of the proportion of those participants who answer "never" to the primary outcome: 'I ask patients if they have missed any doses of their medication' in each country. Using the approach in Cochran,[10] a sample size of 384 health care professionals in each country (128 people in each professional group) would enable estimation of this unknown proportion to within an absolute value of 5% with 95% confidence. Based on previous research,[11] the sample size in each country was inflated to take into account a response rate of 30%.

A mixed-method approach was used to recruit participants in each country, adapted as necessary in each country dependent upon the availability and accessibility of, for example, national registers of healthcare professionals. A random sample of health care professionals was sought from national registers of health care professional bodies or associations. Lists of random numbers were generated using a computer. The random numbers were then used to randomise the national lists of health care professionals and the required number of people selected from each list. Each health care professional that was selected from professional registers initially received a letter inviting them to participate in the online survey and the project information sheet. The invitation letter contained information about the survey as well as the web link which potential participants needed in order to gain access to the survey. Reminder letters were sent to the health care professionals three weeks and again five weeks after the initial contact.

In addition to sending out invitation letters, news articles to promote awareness of the survey were sent to health care professional bodies and associations for circulation through the respective organisations' websites and newsletters. The news article was also distributed to publications whose main audience is health care professionals. The news article contained the same project information and granted access to the survey via the same web link as in the invitation letters and project information sheet.

5.6.2.2 Survey instrument

The questionnaire was designed to elicit information from doctors, nurses and pharmacists about their perceptions of the extent of non-adherence to prescribed medication and their beliefs about and management of non-adherence in patients. There are relatively few research studies examining healthcare professional behaviour with regard to supporting patients with adherence to medication. Although it was not possible to identify any validated scales of healthcare professional behaviour in this domain, two unvalidated but published questionnaires which had been used to measure adherence behaviour among hospital-based doctors[4] and cardiovascular nurses[12] were found. The ABC health care professional adherence questionnaire was informed by a combination of published but unvalidated scales measuring aspects of health care professional behaviour,[4 12] and recommendations for clinical practice from published adherence guidelines.[1, 13-15]

A quantitative self-report questionnaire was designed specifically for this study. A sub-group of the ABC research team discussed, reviewed, and edited potential items considered for inclusion in the questionnaire. The questionnaire comprised of six sections: demographics and health care professionals' characteristics, knowledge of the extent of patient non-adherence, beliefs about adherence to prescribed medicines, use of interventions to improve patient adherence, barriers to the use of interventions to improve patient adherence and previous training received on managing patient non-adherence.

Description of the questionnaire

The questionnaire was made up of eighty-six items in total and divided into five sub-sections. Below is a brief description of each sub-section in the instrument. The questionnaire is included here as Appendix 5.3.

A. Perceptions of the extent of patient non-adherence

This section contains a total of six questions split equally into two subsections. The first section asks about health care professionals' perception of non-adherence in all patients e.g. 'what percentage of **all** patients with a chronic condition/illness in your country do you think do not initiate prescribed medication (that is, patients who do not take any of their prescribed medication)? The second section asks about their perceptions of non-adherence in their own patients e.g. what percentage of **your** patients with a chronic condition/illness in your country do you think do not initiate prescribed medication (that is, patients who do not take any of their prescribed medication)? A five-point rating scale was provided for respondents to make their ratings, with response options of '0 -15%', '16 – 35%', '36 – 65%', '66 -85%', and '86 – 100%'.

B. Beliefs about adherence to medicines

There were seven items in this section. Participants were asked to indicate the extent to which they agree or disagree with each statement about patient adherence. For example, 'it is possible to improve patient adherence to medication'. A five point rating scale was provided for participants to make their ratings, with options ranging from 'strongly disagree' to 'strongly agree' with intermediate labels of 'disagree', 'neither agree nor disagree' and 'agree'. The response category 'don't know' was also available to respondents.

C. Adherence enhancing interventions used by doctors, nurses and pharmacists

This section was made up of a total of fifty questions split into five sub-sections. These were:

(a) Assessment of adherence and its risk factors: There were eight items in this sub-section. An example of an item in this section is: 'I use electronic monitoring devices to assess patient's level of adherence'. The primary outcome wass included in this sub-section. The wording for the question is: 'I ask patients if they have missed any doses of their medication'.

(b) Providing information for carers and patients: There were nine items in this sub-section. An example of an item from this section is: 'I check that patients understand the information that I have given them'.

(c) Talking with patients about their medications: This sub-section was made up of a total of eighteen items. An example of an item from this section is: 'I ask patients what level of involvement they would like in making decisions about their treatment'.

(d) Practical strategies to make medication taking easier: Eleven items made up this sub-section. An example of an item from this section is: 'I help patients to tailor their medication regimen to their own lifestyle'.

(e) Involving others and services to support adherence. This sub-section consisted of four items in total. An example of an item from this section is: 'I refer patients to peer mentor programmes to support medication adherence'.

The response scale is adapted from Berben et al's survey of adherence practices by European cardiovascular nurses.[12] The response options here were split into two. Respondents were first asked to indicate how often they use the intervention. A five-point rating scale was provided for participants to provide their frequency of use with responses ranging from 'never' to 'all the time' and intermediate ratings of 'occasionally', 'sometimes' and 'frequently'. The response category 'not applicable' was made available to participants who do not use any of the interventions mentioned. Next, respondents were given the opportunity to indicate, for every intervention they use, how effective they think that intervention is. A three-point rating scale was provided; with responses ranging from 'not at all' to 'extremely' with an intermediate category 'somewhat'. The response category 'don't know' was provided for those who select the option 'not applicable' to the first question.

D. Barriers to the use of adherence management practices by healthcare professionals

This section contained thirteen questions. An example of an item from the list is: 'I have an excessive workload that prevents me from supporting patients with medicine adherence'. A four-point rating scale was provided for participants to indicate the extent to which the items listed act as barriers to their use of adherence promoting interventions. The options range from 'not at all' to 'very much' with intermediate options of 'slightly' and 'moderately'. The response option 'not applicable' was provided for those who do not consider an item to be relevant to their work setting.

E. A final set of three questions about previous training in medication adherence and use of adherence guidelines completed the questionnaire. The questions asked whether the health care professional has had any training in adherence management during pre-registration or post-registration training. Respondents were also asked if they make use of any practitioner guidelines to manage patient adherence. The response options are 'yes' or 'no'.

Survey administration

The questionnaire was administered online using a web-based survey tool provided by SurveyMonkey.com (http://www.SurveyMonkey.com). Relative to a conventional, paper-based survey, an online survey is cheaper, improves data quality and reduces the time taken to receive

analyzable data.[16 17] For a survey such as this with wide spread geographical coverage use of the internet aids in the logistics of survey administration.

Translation and quality assurance

During the preparation of the study, quality has been ensured through the process of translation and back translation of research questionnaires. The questionnaire and the associated survey materials were translated into the official language(s) for each participating country. The work-flow and quality management processes employed was certified to meet ISO 9001 Quality Management Standards. Forward translations was performed by highly trained, approved and accredited translators who were native speakers of the target languages and fluent in English. Back translations were performed by persons who were native English speakers and fluent in each target language. A third individual acted as a reviewer and highlighted any discrepancies between the forward and back translations and resolved them by discussion with the translators. The respective national coordinators and their teams for each participating country also proofread each translated document and provided feedback on grammatical errors. They also provided contextual interpretation of the translations to ensure that they reflected the appropriate terminology used in each participating country. In addition to this, the online survey was piloted by at least five people in each country in order to check its technical functionality and also to check for comprehensibility, and formatting errors.

Ethics and consent

Ethics approval was provided by the NRES Committee North West Liverpool East (REC Reference 11/NW/0156) for England. The study and ethics protocol approved for England was used as the basis for ethics and research governance for the survey in other European countries and adapted as necessary to meet national ethical requirements. Alterations to the study protocol were only made to ensure ethical conduct in the country concerned or to align the study to local systems and processes for data collection for healthcare professionals.

Respondents who accepted the invitation to the study, and use the link provided to access the survey web page, were taken to the survey introductory page. Here, the participants were provided with information about the project, anonymity of the survey findings, an outline of what participants were required to do and how long it would take to complete the questions, an assurance that every attempt would be made to ensure the confidentiality of the data and a statement indicating that participation is voluntary and that withdrawal from the survey was possible at any stage. Potential participants were asked to click on a link to confirm that they had read the participant information before proceeding. The act of clicking on this link was considered consent to participate in the study. Access to the survey was denied unless this link was clicked.

No personal information (such as names, addresses and professional licence numbers) were collected from participants. The survey was completely anonymous and no IP addresses were stored or downloaded.

5.6.2.3 Statistical analysis

The results of the statistical analysis are reported for the entire sample and for each professional group. The primary outcome was the frequency of assessing the likelihood of non-adherence, based on the response to the question "I ask patients if they have missed any doses of their medication." The number and proportion of participants with the primary outcome are reported. The secondary outcomes were: knowledge of the extent of non-adherence, beliefs about adherence, methods used to support patients with medication taking and barriers to the use of adherence enhancing practices. For the primary outcome, comparisons between countries and professions were performed using multilevel models using the software MLwiN (http://www.cmm.bristol.ac.uk/MLwiN/) for both binary and ordered categories. Responses to the primary outcome were categorised to form a binary variable. Responses of '1' formed one category, which represented healthcare professionals' reports of never having used the intervention, while responses of '2', '3', '4' and '5' were collapsed to form a second category, which represented reports of use of the intervention to some degree. Responses in this latter category were allocated a code of '0'. Participants who indicated that the item was not applicable to their particular role were excluded from the analysis.

5.6.3 Results

Sample demographics

A total of 4967 healthcare professionals started the survey. However, only those who recorded their profession were included in data analysis, resulting in a final sample of 3196 healthcare professionals. Demographic information for the final sample is presented in Table 5.6.

Use of adherence-enhancing interventions

Descriptive statistics are provided for healthcare professionals' use and perceived effectiveness of individual items within each category of adherence-enhancing interventions (see Tables 5.7 and 5.8). Participants who indicated that particular interventions were not relevant to their role were excluded from the analysis and their data are not included within Tables 5.7 and 5.8. For the main analysis of healthcare professionals' use of the interventions, ratings for each item within a section were summed to provide a total rating for each participant, and these were treated as continuous variables. Cronbach's alpha was used to test whether it was appropriate to sum individual item scores within an intervention category and these statistics are reported in the main analysis section. A value of .7 or above was interpreted as indicating satisfactory internal reliability.[18] Total ratings were only calculated for cases where there were no missing data within the section. Means, standard deviations and ranges for the total ratings can be found in Table 5.11.

Beliefs about patients' adherence to medication

Descriptive statistics for healthcare professionals' beliefs about adherence to medication can be found in Table 5.9. Participants who responded with 'do not know' to any of these items were excluded from the analysis and their data are not included within Table 5.9. Cronbach's alpha

indicated that the internal reliability of items assessing healthcare professionals' beliefs about patients' adherence to medication was poor (α = .37). It was therefore inappropriate to calculate total scores for this measure.

Barriers to the use of adherence-enhancing interventions

Prior to the analysis of data on healthcare professionals' perceived barriers to the use of adherence-enhancing interventions, all 'not applicable' responses were excluded. A total rating was calculated for all participants who provided a response to every item on the barriers measure. Cronbach's alpha was used to ensure that it was appropriate to sum the individual item scores. The minimum possible total score was 13, which indicated that none of the items were perceived as barriers to implementing adherence-enhancing interventions, while the maximum possible score of 52 represented the perception that all the barriers described very much inhibited the use of adherence-enhancing interventions. The modal ratings for individual items can be found in Table 5.10, and descriptive statistics for the total score variable are presented in Table 5.11. Data of participants who indicated that particular barriers were not applicable to their role are excluded from the table.

Table 5.6. Demographic information for the final sample

Sample size	Total N = 3196; Austria = 698; Belgium = 289; England = 318; France = 133; Germany = 303; Hungary = 322; Netherlands = 91; Poland = 571; Portugal = 53; Switzerland =418; Doctors = 855; Pharmacists = 1294; Nurses = 1047							
Age (mean and standard deviation)	44.77 (10.96)							
Gender	Male = 1102; Female = 2069							
Years since qualifying (frequency distribution)	Less than one year N = 86	1-5 years N = 354	6-10 years N = 374	11-15 years N = 439	Over 15 years N = 1935			
Type of healthcare setting (frequency distribution)	Community hospital N = 385	Family medication/ general practice N = 820	Specialist community service N = 104	Care/ nursing home N = 155	Community pharmacy/ dispensary N = 1175	Community nursing team N = 154	Polyclinic N = 45	Other N = 308
Type of healthcare organisation (frequency distribution)	Privately funded N = 1127	State funded N = 1050	Insurance/ sick fund funded N = 531	Mixed funded N = 44	Other funding N = 302			
Length of time spent talking to patients about their use of medications (frequency distribution)	No time at all N = 34	Less than one minute N = 158	1-5 minutes N = 1715	6-10 minutes N = 801	11-15 minutes N = 226	More than 15 minutes N = 199		
Pre-registration training in medication adherence management and support (frequency distribution)	Yes N = 296	No N = 1780						
Post-registration training in medication adherence management and support (frequency distribution)	Yes N = 684	No N = 1392						
Any training in medication adherence management and support (frequency distribution)	Yes N = 803	No N = 1268						
Use of practitioner guidelines to assist with management of patient adherence to medication (frequency distribution)	Yes N = 468	No N = 1586						

Table 5.7. Descriptive statistics for healthcare professionals' use of adherence-enhancing interventions

Item	Modal rating for overall sample	Modal rating - doctors	Modal rating - pharmacists	Modal rating - nurses
Assessment of adherence and its risk factors				
I ask patients if they have missed any doses of their medication	4 *(N = 867)* Total N = 2441	4 *(N = 335)* Total N = 705	2 *(N = 328)* Total N = 936	4 *(N = 337)* Total N = 800
I ask patients if they have reduced the dose of their medication	3 *(N = 731)* Total N = 2427	4 *(N = 260)* Total N = 705	2 *(N = 343)* Total N = 936	3 *(N = 254)* Total N = 786
I ask patients if they have changed their medication regimen	3 *(N = 736)* Total N = 2448)	4 *(N = 266)* Total N = 703	3 *(N = 337)* Total N = 951	4 *(N = 242)* Total N = 794
I take blood or urine samples to assess patients' level of adherence	1 *(N = 1150)* Total N = 1808	1 *(N = 342)* Total N = 676	1 *(N = 436)* Total N = 477	1 *(N = 372)* Total N = 655
I use standardised questionnaires/screening tools to assess patients' level of adherence	1 *(N = 1570)* Total N = 2069	1 *(N = 569)* Total N = 676	1 *(N = 525)* Total N = 706	1 *(N = 476)* Total N = 687
I use electronic monitoring devices to assess patients' level of adherence	1 *(N = 1481)* Total N = 1979	1 *(N = 528)* Total N = 664	1 *(N = 489)* Total N = 655	1 *(N = 464)* Total N = 660
I use pill counts to assess patients' level of adherence	1 *(N = 890)* Total N = 2233	1 *(N = 261)* Total N = 691	1 *(N = 383)* Total N = 768	1 *(N = 246)* Total N = 774
I speak to the patients' family, friends or carers to assess the patient's level of adherence	2 *(N = 792)* Total N = 2350	2 *(N = 227)* Total N = 704	2 *(N = 394)* Total N = 854	3 *(N = 279)* Total N = 792
Providing information for patients/carers				
I offer patients information about their condition/illness	4 *(N = 955)* Total N = 2446	5 *(N = 449)* Total N = 708	4 *(N = 429)* Total N = 938	4 *(N = 309)* Total N = 800

I offer patients information about treatment options for their condition/illness	4 *(N = 813)* Total N = 2377	5 *(N = 366)* Total N = 707	4 *(N = 275)* Total N = 907	4 *(N = 278)* Total N = 763
I offer patients information about the medication they are prescribed	5 *(N = 988)* Total N = 2482	5 *(N = 325)* Total N = 706	4 *(N = 421)* Total N = 975	4 *(N = 312)* Total N = 801
I offer patients information about how they might benefit from taking their prescribed medication(s)	4 *(N = 1082)* Total N = 2470	5 *(N = 298)* Total N = 704	4 *(N = 471)* Total N = 972	4 *(N = 327)* Total N = 794
I offer patients information about side effects and how to deal with them	4 *(N = 1009)* Total N = 2484)	4 *(N = 302)* Total N = 707	4 *(N = 414)* Total N = 978)	4 *(N = 293)* Total N = 799
I check that patients understand the information that I have given them	4 *(N = 964)* Total N = 2488	4 *(N = 280)* Total N = 706	4 *(N = 382)* Total N = 972	5 *(N = 337)* Total N = 810
I provide patients with written (paper based) information about their medication	2 *(N = 749)* Total N = 2406	2 *(N = 216)* Total N = 691	2 *(N = 326)* Total N = 965	2 *(N = 207)* Total N = 750
I provide patients with video tapes/DVD/audio/computer materials about their medication	1 *(N = 1785)* Total N = 2199	1 *(N = 551)* Total N = 682	1 *(N = 682)* Total N = 825	1 *(N = 552)* Total N = 692
I offer educational/support classes and peer mentoring to patients	1 *(N = 1292)* Total N = 2148	1 *(N = 388)* Total N = 676	1 *(N = 539)* Total N = 781	1 *(N = 365)* Total N = 691
Talking with patients about their medications				
I ask patients what level of involvement they would like in making decisions about their treatment	1 *(N = 466)* Total N = 1603	2 *(N = 146)* Total N = 517	1 *(N = 268)* Total N = 541	2 *(N = 139)* Total N = 545
I give patients the opportunity to ask any questions about their condition or illness	5 *(N = 1030)* Total N = 2137	5 *(N = 413)* Total N = 644	5 *(N = 282)* Total N = 784	5 *(N = 335)* Total N = 709
I give patients the opportunity to ask questions about their medication	5 *(N = 1188)* Total N = 2203	5 *(N = 359)* Total N = 642	5 *(N = 508)* Total N = 856	5 *(N = 321)* Total N = 705
I address any beliefs or concerns that patients may have which have resulted in non-adherence	4 *(N = 815)* Total N = 2178	4 *(N = 269)* Total N = 640	4 *(N = 277)* Total N = 835	4 *(N = 269)* Total N = 703

I ask patients about their views of whether they need their medication or not, which may have resulted in non-adherence	3 *(N = 581)* Total N = 2109	3 *(N = 178)* Total N = 638	2 *(N = 252)* Total N = 786	4 *(N = 205)* Total N = 685
I ask patients if there are practical reasons (e.g., poor memory, difficulty opening medication bottles) which make it difficult for them to take their medication as prescribed	3 *(N = 616)* Total N = 2181	2 *(N = 189)* Total N = 639	2 *(N = 286)* Total N = 835	4 *(N = 255)* Total N = 707
I discuss with patients what form of support they would like to help them take their medications as prescribed	2 *(N = 630)* Total N = 2165	2 *(N = 210)* Total N = 637	2 *(N = 297)* Total N = 822	4 *(N = 244)* Total N = 706
When patients have difficulty taking their medications as prescribed I suggest solutions which address the specific problems they are having	4 *(N = 794)* Total N = 2175	4 *(N = 236)* Total N = 632	4 *(N = 265)* Total N = 840	4 *(N = 293)* Total N = 703
I offer patients skill building support to increase the patients' capacity to deal with practical aspects of medication-taking (e.g. how to administer injectable drugs)	4 *(N = 575)* Total N = 2067	4 *(N = 160)* Total N = 630	4 *(N = 200)* Total N = 764	4 *(N = 215)* Total N = 673
I review treatment goals with patients and incorporate medication adherence into the review	4 *(N = 435)* Total N = 1718	4 *(N = 207)* Total N = 574	2 *(N = 215)* Total N = 611	4 *(N = 146)* Total N = 533
I encourage involvement of patients in their own care through self-monitoring (e.g. recording glucose levels in diabetic patients)	4 *(N = 805)* Total N = 2090	4 *(N = 296)* Total N = 631	4 *(N = 229)* Total N = 769	4 *(N = 280)* Total N = 690
I use reinforcement to support patients to continue to take their medication e.g. assessment of adherence with patient feedback	4 *(N = 707)* Total N = 2089	4 *(N = 247)* Total N = 632	4 *(N = 216)* Total N = 769	4 *(N = 244)* Total N = 688
I discuss any options available for reducing the cost of the prescription for the patient	4 *(N = 492)* Total N = 1491	4 *(N = 153)* Total N = 377	4 *(N = 197)* Total N = 583	4 *(N = 142)* Total N = 531
I offer rewards for improved adherence and/or treatment response (e.g. reduced frequency of visits; partial payment for equipment)	1 *(N = 1145)* Total N = 1602	1 *(N = 428)* Total N = 597	1 *(N = 410)* Total N = 481	1 *(N = 307)* Total N = 524
I use a motivational style (such as motivational interviewing) when discussing medication taking with patients	4 *(N = 599)* Total N = 2023	4 *(N = 197)* Total N = 627	4 *(N = 206)* Total N = 737	4 *(N = 196)* Total N = 659
I use a cognitive-behavioural style when discussing medication-	2 *(N = 497)*	2 *(N = 177)*	2 *(N = 187)*	3 *(N = 173)*

taking with patients	Total N = 1872	Total N = 593	Total N = 657	Total N = 622
I use an educational style when discussing medication-taking with patients	4 *(N = 755)* Total N = 2083	4 *(N = 251)* Total N = 631	4 *(N = 268)* Total N = 784	4 *(N = 236)* Total N = 668
I schedule more frequent appointments when patients have problems with medication adherence	4 *(N = 465)* Total N = 1629	4 *(N = 234)* Total N = 629	1 *(N = 198)* Total N = 438	4 *(N = 190)* Total N = 562
Practical strategies to make medication taking easier				
I recommend the medication regimen is simplified by reducing administration frequency (e.g. by use of long acting drugs)	4 *(N = 541)* Total N = 1601	4 *(N = 336)* Total N = 597	2 *(N = 173)* Total N = 498	3 *(N = 154)* Total N = 506
I recommend the medication regimen is simplified by the use of combination drugs	4 *(N = 450)* Total N = 1579	4 *(N = 307)* Total N = 603	2 *(N = 210)* Total N = 500	1 *(N = 139)* Total N = 476
I recommend the medication regimen is simplified by reducing the use of multiple medication for a single condition	3 *(N = 405)* Total N = 1561	4 *(N = 248)* Total N = 597	2 *(N = 163)* Total N = 487	1 *(N = 144)* Total N = 477
I recommend the use of the medication formulation most appropriate for each patient (e.g. oral tablet, oral solution, IV injection, patch)	4 *(N = 596)* Total N = 1732	4 *(N = 276)* Total N = 607	2 *(N = 192)* Total N = 572	4 *(N = 183)* Total N = 553
I recommend the use of medication in packaging patients will find easy to use	2 *(N = 486)* Total N = 1704	2 *(N = 169)* Total N = 579	2 *(N = 205)* Total N = 611	4 *(N = 120)* Total N = 514
I help patients to tailor their medication regimen to their own lifestyle	4 *(N = 590)* Total N = 1813	4 *(N = 249)* Total N = 605	2 *(N = 196)* Total N = 631	4 *(N = 200)* Total N = 577
I help patients to use cueing (taking medication in combination with routine behaviours, such as meals, television programmes, brushing teeth in the morning)	4 *(N = 724)* Total N = 1973	4 *(N = 229)* Total N = 607	4 *(N = 246)* Total N = 727	4 *(N = 249)* Total N = 639
I recommend reminder systems to patients such as pagers, mobile phone, alarm watches, telephone services, calendars	2 *(N = 645)* Total N = 1964	2 *(N = 221)* Total N = 601	2 *(N = 282)* Total N = 733	3 *(N = 198)* Total N = 630
I recommend medication charts and diaries to patients to help them remember and record when they have taken their medication	2 *(N = 631)* Total N = 1971	2 *(N = 200)* Total N = 600	2 *(N = 275)* Total N = 746	3 *(N = 164)* Total N = 625

I recommend dispensers for organising medication, e.g. pillboxes, monitored dosage systems	4 *(N = 888)* Total N = 2035	4 *(N = 296)* Total N = 609	4 *(N = 321)* Total N = 764	4 *(N = 271)* Total N = 662
I form adherence contracts with patients that describe what the patient, carers and healthcare professionals will do to support the patients' medication adherence	1 *(N = 1110)* Total N = 1559	1 *(N = 415)* Total N = 582	1 *(N = 382)* Total N = 459	1 *(N = 313)* Total N = 518
Involving others, and other services, to support adherence				
I encourage involvement of family or carers in strategies and interventions for medication adherence	2 *(N = 593)* Total N = 1908	2 *(N = 196)* Total N = 604	2 *(N = 280)* Total N = 654	4 *(N = 218)* Total N = 650
I arrange medication counselling by a specialist for patients to support medication adherence	1 *(N = 955)* Total N = 1595	1 *(N = 353)* Total N = 585	1 *(N = 353)* Total N = 480	1 *(N = 249)* Total N = 530
I refer patients to peer mentor programmes to support medication adherence	1 *(N = 1058)* Total N = 1639	1 *(N = 390)* Total N = 583	1 *(N = 363)* Total N = 527	1 *(N = 305)* Total N = 529
I refer to case management services for high risk patients to support medication adherence	1 *(N = 1019)* Total N = 1538	1 *(N = 371)* Total N = 563	1 *(N = 357)* Total N = 481	1 *(N = 291)* Total N = 494

Note. Response scale: 1 = Never; 2 = Occasionally; 3 = Sometimes; 4 = Frequently; 5 = All the time

Table 5.8. Descriptive statistics for the perceived effectiveness of adherence-enhancing interventions

Item	Modal rating for overall sample	Modal rating - doctors	Modal rating - pharmacists	Modal rating - nurses
Assessment of adherence and its risk factors				
I ask patients if they have missed any doses of their medication	2 *(N = 1487)* Total N = 2425	2 *(N = 450)* Total N = 699	2 *(N = 584)* Total N = 927	2 *(N = 453)* Total N = 799
I ask patients if they have reduced the dose of their medication	2 *(N = 1394)* Total N = 2354	2 *(N = 412)* Total N = 688	2 *(N = 538)* Total N = 912	2 *(N = 444)* Total N = 754
I ask patients if they have changed their medication regimen	2 *(N = 1379)* Total N = 2398	2 *(N = 400)* Total N = 689	2 *(N = 562)* Total N = 937	2 *(N = 417)* Total N = 772
I take blood or urine samples to assess patients' level of adherence	4 *(N = 666)* Total N = 1698	2 *(N = 195)* Total N = 596	4 *(N = 317)* Total N = 515	4 *(N = 200)* Total N = 587
I use standardised questionnaires/screening tools to assess patients' level of adherence	4 *(N = 810)* Total N = 1741	4 *(N = 228)* Total N = 523	4 *(N = 321)* Total N = 640	4 *(N = 261)* Total N = 578
I use electronic monitoring devices to assess patients' level of adherence	4 *(N = 798)* Total N = 1701	4 *(N = 228)* Total N = 538	4 *(N = 330)* Total N = 615	4 *(N = 240)* Total N = 548
I use pill counts to assess patients' level of adherence	2 *(N = 891)* Total N = 2097	2 *(N = 292)* Total N = 630	2 *(N = 278)* Total N = 747	2 *(N = 321)* Total N = 720
I speak to the patients' family, friends or carers to assess the patient's level of adherence	2 *(N = 1357)* Total N = 2310	2 *(N = 431)* Total N = 686	2 *(N = 477)* Total N = 844	2 *(N = 449)* Total N = 780
Providing information for patients/carers				
I offer patients information about their condition/illness	3 *(N = 1132)* Total N = 2447	3 *(N = 400)* Total N = 698	2 *(N = 501)* Total N = 965	3 *(N = 378)* Total N = 784
I offer patients information about treatment options for their	2 *(N = 1202)*	3 *(N = 330)*	2 *(N = 513)*	2 *(N = 363)*

condition/illness	Total N = 2376	Total N = 695	Total N = 931	Total N = 750
I offer patients information about the medication they are prescribed	3 *(N = 1134)* Total N = 2449	2 *(N = 367)* Total N = 698	3 *(N = 492)* Total N = 973	3 *(N = 360)* Total N = 778
I offer patients information about how they might benefit from taking their prescribed medication(s)	3 *(N = 1125)* Total N = 2426	2 *(N = 336)* Total N = 691	3 *(N = 444)* Total N = 962	3 *(N = 365)* Total N = 773
I offer patients information about side effects and how to deal with them	2 *(N = 1258)* Total N = 2438	2 *(N = 391)* Total N = 696	2 *(N = 502)* Total N = 975	2 *(N = 365)* Total N = 767
I check that patients understand the information that I have given them	3 *(N = 1085)* Total N = 2443	2 *(N = 344)* Total N = 695	3 *(N = 437)* Total N = 966	3 *(N = 383)* Total N = 782
I provide patients with written (paper based) information about their medication	2 *(N = 1153)* Total N = 2282	2 *(N = 314)* Total N = 636	2 *(N = 501)* Total N = 945	2 *(N = 338)* Total N = 701
I provide patients with video tapes/DVD/audio/computer materials about their medication	4 *(N = 862)* Total N = 1647	4 *(N = 238)* Total N = 506	4 *(N = 361)* Total N = 632	4 *(N = 263)* Total N = 509
I offer educational/support classes and peer mentoring to patients	4 *(N = 666)* Total N = 1733	2 *(N = 201)* Total N = 542	4 *(N = 297)* Total N = 651	2 *(N = 207)* Total N = 540
Talking with patients about their medications				
I ask patients what level of involvement they would like in making decisions about their treatment	2 *(N = 617)* Total N = 1423	2 *(N = 214)* Total N = 471	2 *(N = 180)* Total N = 476	2 *(N = 223)* Total N = 476
I give patients the opportunity to ask any questions about their condition or illness	3 *(N = 1072)* Total N = 2108	2 *(N = 360)* Total N = 628	2 *(N = 362)* Total N = 788	3 *(N = 384)* Total N = 692
I give patients the opportunity to ask questions about their medication	3 *(N = 1160)* Total N = 2159	3 *(N = 302)* Total N = 629	3 *(N = 497)* Total N = 843	3 *(N = 361)* Total N = 687
I address any beliefs or concerns that patients may have which have resulted in non-adherence	2 *(N = 1057)* Total N = 2126	2 *(N = 334)* Total N = 626	2 *(N = 398)* Total N = 824	2 *(N = 325)* Total N = 676
I ask patients about their views of whether they need their medication	2 *(N = 1005)*	2 *(N = 309)*	2 *(N = 360)*	2 *(N = 336)*

or not, which may have resulted in non-adherence	Total N = 1990	Total N = 606	Total N = 743	Total N = 641
I ask patients if there are practical reasons (e.g., poor memory, difficulty opening medication bottles) which make it difficult for them to take their medication as prescribed	2 *(N = 1079)* Total N = 2101	2 *(N = 355)* Total N = 612	2 *(N = 427)* Total N = 821	3 *(N = 305)* Total N = 668
I discuss with patients what form of support they would like to help them take their medications as prescribed	2 *(N = 1022)* Total N = 2054	2 *(N = 320)* Total N = 594	2 *(N = 404)* Total N = 789	2 *(N = 298)* Total N = 671
When patients have difficulty taking their medications as prescribed I suggest solutions which address the specific problems they are having	3 *(N = 986)* Total N = 2131	2 *(N = 318)* Total N = 615	3 *(N = 384)* Total N = 833	3 *(N = 352)* Total N = 683
I offer patients skill building support to increase the patients' capacity to deal with practical aspects of medication-taking (e.g. how to administer injectable drugs)	3 *(N = 907)* Total N = 1966	2 *(N = 260)* Total N = 590	3 *(N = 330)* Total N = 752	3 *(N = 327)* Total N = 624
I review treatment goals with patients and incorporate medication adherence into the review	2 *(N = 801)* Total N = 1648	2 *(N = 272)* Total N = 549	2 *(N = 266)* Total N = 603	2 *(N = 263)* Total N = 496
I encourage involvement of patients in their own care through self-monitoring (e.g. recording glucose levels in diabetic patients)	3 *(N = 943)* Total N = 2047	3 *(N = 309)* Total N = 614	2 *(N = 366)* Total N = 777	3 *(N = 346)* Total N = 656
I use reinforcement to support patients to continue to take their medication e.g. assessment of adherence with patient feedback	2 *(N = 1023)* Total N = 1994	2 *(N = 306)* Total N = 595	2 *(N = 376)* Total N = 747	2 *(N = 341)* Total N = 652
I discuss any options available for reducing the cost of the prescription for the patient	2 *(N = 620)* Total N = 1430	2 *(N = 165)* Total N = 366	2 *(N = 243)* Total N = 557	2 *(N = 212)* Total N = 507
I offer rewards for improved adherence and/or treatment response (e.g. reduced frequency of visits; partial payment for equipment)	4 *(N = 596)* Total N = 1306	4 *(N = 164)* Total N = 455	4 *(N = 271)* Total N = 433	4 *(N = 161)* Total N = 632
I use a motivational style (such as motivational interviewing) when discussing medication taking with patients	2 *(N = 940)* Total N = 1943	2 *(N = 294)* Total N = 587	2 *(N = 336)* Total N = 735	2 *(N = 310)* Total N = 621
I use a cognitive-behavioural style when discussing medication-taking with patients	2 *(N = 893)* Total N = 1769	2 *(N = 283)* Total N = 540	2 *(N = 297)* Total N = 655	2 *(N = 313)* Total N = 574

I use an educational style when discussing medication-taking with patients	2 *(N = 1132)* Total N = 2032	2 *(N = 352)* Total N = 612	2 *(N = 417)* Total N = 795	2 *(N = 363)* Total N = 625
I schedule more frequent appointments when patients have problems with medication adherence	2 *(N = 835)* Total N = 1659	2 *(N = 388)* Total N = 610	4 *(N = 211)* Total N = 502	2 *(N = 272)* Total N = 547
Practical strategies to make medication taking easier				
I recommend the medication regimen is simplified by reducing administration frequency (e.g. by use of long acting drugs)	2 *(N = 727)* Total N = 1651	3 *(N = 309)* Total N = 581	2 *(N = 253)* Total N = 561	2 *(N = 218)* Total N = 509
I recommend the medication regimen is simplified by the use of combination drugs	2 *(N = 742)* Total N = 1600	2 *(N = 286)* Total N = 584	2 *(N = 259)* Total N = 547	2 *(N = 197)* Total N = 469
I recommend the medication regimen is simplified by reducing the use of multiple medication for a single condition	2 *(N = 778)* Total N = 1582	2 *(N = 325)* Total N = 583	2 *(N = 246)* Total N = 534	2 *(N = 207)* Total N = 465
I recommend the use of the medication formulation most appropriate for each patient (e.g. oral tablet, oral solution, IV injection, patch)	2 *(N = 791)* Total N = 1772	2 *(N = 285)* Total N = 593	2 *(N = 283)* Total N = 625	3 *(N = 232)* Total N = 554
I recommend the use of medication in packaging patients will find easy to use	2 *(N = 835)* Total N = 1696	2 *(N = 320)* Total N = 552	2 *(N = 316)* Total N = 642	2 *(N = 199)* Total N = 502
I help patients to tailor their medication regimen to their own lifestyle	2 *(N = 903)* Total N = 1797	2 *(N = 307)* Total N = 583	2 *(N = 339)* Total N = 658	2 *(N = 257)* Total N = 556
I help patients to use cueing (taking medication in combination with routine behaviours, such as meals, television programmes, brushing teeth in the morning)	2 *(N = 989)* Total N = 1909	2 *(N = 331)* Total N = 585	2 *(N = 373)* Total N = 727	2 *(N = 285)* Total N = 597
I recommend reminder systems to patients such as pagers, mobile phone, alarm watches, telephone services, calendars	2 *(N = 972)* Total N = 1805	2 *(N = 306)* Total N = 551	2 *(N = 364)* Total N = 690	2 *(N = 302)* Total N = 564
I recommend medication charts and diaries to patients to help them remember and record when they have taken their medication	2 *(N = 931)* Total N = 1784	2 *(N = 294)* Total N = 534	2 *(N = 358)* Total N = 696	2 *(N = 279)* Total N = 554
I recommend dispensers for organising medication, e.g. pillboxes,	3 *(N = 1002)*	2 *(N = 277)*	2, 3 *(N = 354)*	3 *(N = 379)*

monitored dosage systems	Total N = 1965	Total N = 586	Total N = 756	Total N = 623
I form adherence contracts with patients that describe what the patient, carers and healthcare professionals will do to support the patients' medication adherence	4 *(N = 628)* Total N = 1305	4 *(N = 190)* Total N = 458	4 *(N = 273)* Total N = 429	4 *(N = 165)* Total N = 418
Involving others, and other services, to support adherence				
I encourage involvement of family or carers in strategies and interventions for medication adherence	2 *(N = 993)* Total N = 1833	2 *(N = 335)* Total N = 571	2 *(N = 350)* Total N = 644	2 *(N = 308)* Total N = 618
I arrange medication counselling by a specialist for patients to support medication adherence	4 *(N = 534)* Total N = 1336	2 *(N = 180)* Total N = 469	4 *(N = 231)* Total N = 439	2 *(N = 179)* Total N = 428
I refer patients to peer mentor programmes to support medication adherence	4 *(N = 580)* Total N = 1291	4 *(N = 181)* Total N = 444	4 *(N = 251)* Total N = 458	2 *(N = 154)* Total N = 389
I refer to case management services for high risk patients to support medication adherence	4 *(N = 635)* Total N = 1273	4 *(N = 196)* Total N = 443	4 *(N = 258)* Total N = 431	4 *(N = 181)* Total N = 399

Note. Response scale: 1 = Not at all; 2 = Somewhat; 3 = Extremely; 4 = Do not know

Table 5.9. Descriptive statistics for healthcare professionals' beliefs about patients' adherence to medication

Item	Modal rating for overall sample	Modal rating - doctors	Modal rating - pharmacists	Modal rating - nurses
Patients' beliefs about whether or not they need medication affect their adherence to treatment	5 *(N = 1596)* Total N = 2782	5 *(N = 435)* Total N = 768	5 *(N = 719)* Total N = 1112	5 *(N = 442)* Total N = 902
Patients' concerns about their medication affect their adherence to treatment	5 *(N = 1451)* Total N = 2799	5 *(N = 422)* Total N = 768	5 *(N = 660)* Total N = 1111	4 *(N = 454)* Total N = 920
Most non-adherence is intentional	4 *(N = 965)* Total N = 2719	4 *(N = 293)* Total N = 750	4 *(N = 370)* Total N = 1080	4 *(N = 302)* Total N = 889
Most non-adherence is unintentional	4 *(N = 860)* Total N = 2696	2 *(N = 263)* Total N = 740	4 *(N = 354)* Total N = 1075	4 *(N = 298)* Total N = 881
It is possible to improve patient adherence to medication	4 *(N = 1336)* Total N = 2747	4 *(N = 389)* Total N = 753	5 *(N = 567)* Total N = 1104	4 *(N = 464)* Total N = 900
There is not one specific intervention for improving adherence which is suitable for everyone	4 *(N = 1079)* Total N = 2697	4 *(N = 283)* Total N = 745	4 *(N = 420)* Total N = 1078	4 *(N = 376)* Total N = 874
Patients have the right to refuse or to stop taking medication providing they have the capacity to make informed decisions	5 *(N = 1278)* Total N = 2772	5 *(N = 437)* Total N = 762	4 *(N = 443)* Total N = 1100	5 *(N = 411)* Total N = 910

Note. Response scale: 1 = Strongly disagree; 2 = Disagree; 3 = Neither agree nor disagree; 4 = Agree; 5 = Strongly agree

Table 5.10. Descriptive statistics for healthcare professionals' perceived barriers to the use of adherence-enhancing interventions

Item	Modal rating for overall sample	Modal rating - doctors	Modal rating - pharmacists	Modal rating - nurses
I find it difficult identifying non-adherence in my patients	2 *(N = 797)* Total N = 2009	2 *(N = 251)* Total N = 597	2 *(N = 282)* Total N = 751	2 *(N = 264)* Total N = 661
I lack experience in the use of adherence management practices	2 *(N = 635)* Total N = 1881	2 *(N = 192)* Total N = 544	2 *(N = 243)* Total N = 700	2 *(N = 200)* Total N = 637
I have limited access to evidence-based information about which adherence enhancing interventions are beneficial under what circumstances	2 *(N = 576)* Total N = 1905	2 *(N = 179)* Total N = 561	3 *(N = 215)* Total N = 723	2 *(N = 197)* Total N = 621
I had no or limited opportunity to study adherence management during pre-qualification training	4 *(N = 771)* Total N = 1879	4 *(N = 273)* Total N = 569	4 *(N = 294)* Total N = 714	4 *(N = 204)* Total N = 596
I have no or limited opportunity to study adherence management post-qualification	3 *(N = 547)* Total N = 1826	3 *(N = 166)* Total N = 548	3 *(N = 222)* Total N = 703	3 *(N = 159)* Total N = 575
I lack training in managing long-term conditions	1 *(N = 675)* Total N = 1783	1 *(N = 232)* Total N = 516	1 *(N = 219)* Total N = 679	1 *(N = 224)* Total N = 588
Lack of a co-ordinated approach by all the healthcare providers involved in a patient's care prevents me from supporting patients with medication adherence	4 *(N = 532)* Total N = 1881	2 *(N = 179)* Total N = 544	4 *(N = 290)* Total N = 725	2 *(N = 198)* Total N = 612
Lack of continuity of patient care prevents me from supporting patients with medication adherence	2 *(N = 570)* Total N = 1883	1 *(N = 182)* Total N = 557	3 *(N = 214)* Total N = 701	1 *(N = 194)* Total N = 625
I have an excessive workload that prevents me from supporting patients with medication adherence	2 *(N = 642)* Total N = 1902	2 *(N = 191)* Total N = 566	2 *(N = 234)* Total N = 712	2 *(N = 217)* Total N = 624
I have short consultation times with patients that prevent me from supporting patients with medication adherence	2 *(N = 543)* Total N = 1745	2 *(N = 158)* Total N = 562)	2 *(N = 194)* Total N = 603	2 *(N = 191)* Total N = 580
I have difficulty involving patients in decisions about their medication	1 *(N = 691)*	1 *(N = 258)*	1 *(N = 199)*	1 *(N = 234)*

	Total N = 1733	Total N = 547	Total N = 613	Total N = 573
There are inadequate resources available in the healthcare system to enable me to support medication adherence	2 *(N = 583)* Total N = 1876	4 *(N = 180)* Total N = 567	4 *(N = 228)* Total N = 704	2 *(N = 216)* Total N = 605
There is a lack of performance-based payment incentives to encourage me to support adherence	4 *(N = 540)* Total N = 1681	4 *(N = 160)* Total N = 525	4 (N = 238) Total N = 652	1 *(N = 178)* Total N = 504

Note. Response scale: 1 = Not at all; 2 = Slightly; 3 = Moderately; 4 = Very much

Table 5.11. Descriptive statistics for total scores on healthcare professionals' use of, and perceived barriers to the use of, adherence-enhancing interventions

Variable	Mean (SD) and range for overall sample	Mean (SD) and range - doctors	Mean (SD) and range – pharmacists	Mean (SD) and range - nurses
Assessment of adherence and its risk factors (Minimum possible score = 8 ; maximum possible score = 40)	19.00 (4.79) 8-35 N = 1690	19.59 (4.28) 8-35 N = 642	16.25 (4.26) 8-31 N = 463	20.52 (4.83) 8-35 N = 585
Providing information for patients/carers (Minimum possible score = 9 ; maximum possible score = 45)	28.90 (5.64) 9-44 N = 2002	30.40 (4.90) 9-44 N = 656	27.67 (5.12) 9-42 N = 704	28.71 (6.48) 9-44 N = 642
Talking with patients about their medications (Minimum possible score = 18 ; maximum possible score = 90)	55.87 (11.32) 21-87 N = 555	56.15 (9.16) 33-81 N = 172	50.61 (10.99) 27-77 N = 175	60.07 (11.44) 21-87 N = 208
Practical strategies to make medication taking easier (Minimum possible score = 11 ; maximum possible score = 55)	30.72 (7.52) 11-55 N = 1260	33.29 (6.12) 17-54 N = 532	27.08 (6.50) 11-47 N = 358	30.54 (8.71) 11-55 N = 370
Involving others, and other services, to support adherence (Minimum possible score = 4 ; maximum possible score = 20)	7.47 (2.79) 4-19 N = 1420	7.55 (2.69) 4-18 N = 551	6.32 (2.18) 4-16 N = 415	8.44 (3.02) 4-19 N = 454
Perceived barriers to the use of adherence-enhancing interventions (Minimum possible score = 13 ; maximum possible score = 52)	31.51 (8.39) 13-52 N = 1097	31.55 (7.65) 13-49 N = 382	33.14 (8.03) 13-52 N = 382	29.59 (9.19) 13-51 N = 333

5.6.3.1 Main analyses

Primary outcome

Multiple logistic regression

The objective in this section is to evaluate the effect on the primary outcome of groups of predictor variables in three areas, namely demographics, professional practice, and beliefs and perceptions. The group of demographics variables comprised gender and age of respondents, while professional practice encompassed number of years registered as a qualified healthcare professional, the average amount of time spent talking with patients about their use of medications, any pre-registration or post-registration training in medication adherence management and support, and the use of practitioner guidelines to assist with the management of patients' adherence. Variables included within the beliefs and perceptions category included perceptions of the extent of non-initiation of prescribed medication for all patients within the respondent's nation, optimistic bias for perceptions of non-initiation within one's own patients, and total scores for perceived barriers to the use of adherence-enhancing interventions. The effect of profession on the primary outcome variable was also assessed. Multiple logistic regression was used taking into account the hierarchical nature of the data and the results are presented as Odds Ratios (ORs) and their 95% confidence intervals. Where there are ordinal responses the lowest is taken as the comparator value and ORs are presented for the binary responses for categorical variables, for instance the use of practitioner guidelines to assist with the management of patient adherence. Where there are variables measured over a more extensive range, such as age, then ORs represent the change per unit (per year for age). Where there appears to be a trend in the predictors this is tested.

Post hoc it was found that the frequency of the primary outcome (never asking patients if they had missed any doses of their medication) produced a relatively small number of responses; consequently a further analysis was carried out using the binary outcome where patients were asked frequently or all the time about missed doses.

The software used for the analysis was MLwiN (version 2.25, Centre for Multilevel Modelling, University of Bristol, February 2012) with three levels (country, profession and individual). Logistic regressions were applied with random intercepts which were allowed to vary at both the country and profession level and fixed effects for all variables within the three groups. A preliminary analysis where the intercept was allowed to vary at the country level and with a profession fixed effect is also given. In practice in most cases the country effects were not significant and models were refitted with only profession random effects. The results are presented for both outcomes in Tables 5.12 and 5.13.

Profession fixed effect/country random effect

The results in this section are consistent for the two versions of the primary outcome. The ORs and their confidence intervals suggest that pharmacists are approximately 2.8 times more likely to have a

never response than doctors, and the doctors and nurses are not significantly different. Pharmacists are also approximately 4.6 times less likely to ask patients frequently or all the time.

Demographics/profession random effect

The country random effect was found to be non-significant. Both age and gender were found to have non-significant effects with ORs near 1 and 95% confidence intervals containing 1.

Table 5.12: Results of multiple logistic regression for never asking patients about missed doses as the dependent variable

Variable		OR	95% CI
Profession*	Doctor	1.00	
	Pharmacist	2.80	1.71 – 4.58
	Nurse	0.92	0.50 – 1.69
*Demographics***			
Gender	Male	1.00	
	Female	0.91	0.59 – 1.43
Age	Per year	1.02	0.84 – 1.24
*Professional practice***			
Number of years registered as a qualified healthcare professional	Less than 1 year	1.00	
	1-5 years	0.22	0.07 – 0.71
	6-10 years	0.40	0.14 – 1.17
	11-15 years	0.31	0.10 – 0.92
	Over 15 years	0.22	0.08 – 0.60
Time spent talking with patients about their use of medications	No time at all	1.00	
	Less than one minute	0.63	0.13 – 3.19
	1-5 minutes	0.18	0.04 – 0.84
	6-10 minutes	0.05	0.01 – 0.27
	11-15 minutes	0.08	0.01 – 0.57
	More than 15 minutes	0.11	0.02 – 0.71
Pre-registration and/or post-registration training in adherence management and support	No	1.00	
	Yes	0.59	0.33 – 1.06
Use of practitioner guidelines to assist with management of patient adherence to medication	No	1.00	
	Yes	0.82	0.42 – 1.58

*Beliefs and perceptions***			
Estimated percentage of all patients within your nation who do not initiate prescribed medication	0 – 15%	1.00	
	16 – 35%	1.32	0.62 – 2.84
	36 – 65%	2.17	0.73 – 6.42
	66 - 100%	4.28	0.83 – 22.08
Difference score for estimated percentage of all patients within your nation who do not initiate prescribed medication subtracted from estimated percentage of patients that you see who do not initiate prescribed medication	< = -2	1.00	
	-1	1.96	0.40 – 9.55
	0	1.03	0.22 – 4.87
	1	2.87	0.21 – 39.01
	> = 2	3.10	0.49 – 19.52
Total score for perceived barriers to implementing adherence-enhancing interventions	Per unit increase	1.05	1.01 – 1.09

* intercept allowed to vary by country; ** intercept allowed to vary by profession

Table 5.13: Results of multiple logistic regression for asking patients about missed doses frequently or all the time as the dependent variable

Variable		OR	95% CI
Profession*	Doctor	1.00	
	Pharmacist	0.22	0.17 – 0.27
	Nurse	1.12	0.90 – 1.41
*Demographics***			
Gender	Male	1.00	
	Female	1.02	0.84 – 1.23
Age	Per year	1.01	1.00 – 1.01
*Professional practice***			
Number of years registered as a qualified healthcare professional	Less than 1 year	1.00	
	1-5 years	2.19	1.09 – 4.38
	6-10 years	2.32	1.16 – 4.63
	11-15 years	1.90	0.96 – 3.77
	Over 15 years	2.08	1.08 – 4.00
Time spent talking with patients about their use of medications	No time at all	1.00	
	Less than one minute	3.69	0.72 – 18.95
	1-5 minutes	3.88	0.80 – 18.89
	6-10 minutes	6.12	1.25 – 29.95
	11-15 minutes	8.40	1.67 – 42.31
	More than 15 minutes	9.10	1.80 – 46.01

Pre-registration and/or post-registration training in adherence management and support	No	1.00	
	Yes	1.42	1.16 – 1.74
Use of practitioner guidelines to assist with management of patient adherence to medication	No	1.00	
	Yes	1.21	0.96 – 1.52
*Beliefs and perceptions***			
Estimated percentage of all patients within your nation who do not initiate prescribed medication	0 – 15%	1.00	
	16 – 35%	0.70	0.49 – 1.00
	36 – 65%	0.76	0.42 – 1.36
	66 - 100%	1.37	0.47 – 4.05
Difference score for estimated percentage of all patients within your nation who do not initiate prescribed medication subtracted from estimated percentage of patients that you see who do not initiate prescribed medication	< = -2	1.00	
	-1	1.73	0.69 – 4.32
	0	0.98	0.39 – 2.47
	1	1.10	0.37 – 3.23
	> = 2	1.00	0.27 – 3.77
Total score for perceived barriers to implementing adherence-enhancing interventions	Per unit increase	0.94	0.93 – 0.96

* intercept allowed to vary by country; ** intercept allowed to vary by profession

Professional practice/profession random effect

Length of time registered as a qualified healthcare professional appears to have a positive effect on both outcomes when compared to the less than one year qualified. This is more marked for the never asked outcome; there is no discernible trend however over the categories. For length of time spent talking with patients about their use of medications, there is a significant trend downwards (OR=.524 per unit change, 95% confidence interval, 0.36- 0.727) and upwards (OR=1.42 per unit change, 95% confidence interval, 1.27- 1.57). Training, which was a binary variable reflecting any pre-registration and/or post-registration training in medication adherence management and support, has a nearly significant effect for the never category, where those with training are approximately 60% less likely to never ask patients about missed doses. For the frequently/always outcome, training predicts an approximately 42% increase in this outcome. The use of practitioner guidelines to assist with the management of patient adherence to medication does not reach significance but point estimates of the ORs indicate similar positive effects for both outcomes.

Beliefs and perceptions/profession random effects

The largest and smallest values for the differences between healthcare professionals' perceptions of the extent of non-initiation of prescribed medication in their own patients and in patients in general within their nation were collapsed because of sparse data. There were also few observations for the largest values for healthcare professionals' perceptions of the extent of non-initiation in patients in general within their nations, so these values were collapsed to form a single category. There were no significant effects of the difference scores, representing optimistic bias for non-initiation within healthcare professionals' own patients, or perceptions of non-initiation for patients in general within the healthcare professionals' nations on either version of the primary outcome. There was, however, a significant effect of perceived barriers to the use of adherence-enhancing interventions for both outcomes. The model predicted an approximately 5% increase in the possibility of a never response and an approximately 5% decrease in a frequently/all the time response per unit increase in total barriers score.

Use of adherence-enhancing interventions

Internal reliability of measures

Cronbach's alphas indicated that the items assessing 'providing information for patients/carers' (α = .80), 'talking with patients about their medications' (α = .87), 'practical strategies to make medication taking easier' (α = .83), and 'involving others, and other services, to support adherence (α = .72) showed good internal reliability. The internal reliability of the measure for 'assessment of adherence and its risk factors' fell marginally below the accepted level of .70 (α = .69). Results derived from the total ratings for this section should therefore be interpreted with caution. The measure of perceived barriers to the use of adherence-enhancing interventions showed good internal reliability (α = .86).

Some categories of interventions were found to correlate with each other, using Pearson's r with a cut-off level of 0.5. Higher scores for frequency of use of assessment interventions were found to correlate with higher scores for the use of interventions focussed on talking with patients about their

medications (r = 0.53). High scores for the use of interventions focussed on talking with patients about their medications were also correlated with higher reported use of practical strategies to make medication taking easier (r = 0.58).

Structure of analysis

Three series of between-subjects analysis of variance (ANOVA) were conducted in the analysis of data on healthcare professionals' use of adherence-enhancing interventions and perceived barriers to the use of interventions for adherence. First, a series of ANOVAs are reported for the main effects of profession and nation on healthcare professionals' total ratings for each of the five categories of adherence-enhancing interventions and perceived barriers to implementing interventions for adherence. Data for all professions and all participating nations were included in these analyses. To enable testing for potential interactions between profession and nation for each of the outcome variables, a second series of ANOVAs is reported. As data were not collected from nurses in France and Germany, the data from these nations were excluded in this second series of analyses. Finally, a third series of ANOVAs are reported, which address the problem of a small sample size for Portugal by excluding Portuguese data, in addition to the data from France and Germany. Although it is acknowledged that this sequence of analyses represents multiple testing of a single data set, it was possible to explore the data in a number of ways and all analyses are reported for completeness. The sample sizes for the first two analyses were considered to be large enough so that normality based tests were appropriate, however inferences were checked using the non-parametric Kruskall-Wallis test.

Analysis of variance: Main effects

All analyses were carried out using NCSS 2007 (version 07.1.19, J. Hintze (2009) Kaysville Utah USA). Initially, a series of 3 x 10 between-subjects ANOVAs using the General Linear Model (GLM) procedures were conducted to examine the main effects of profession and nation on total scores for healthcare professionals' use of adherence-enhancing interventions for each category of intervention. These analyses were conducted on the data of those participants who had indicated their profession, across all 10 countries involved in the survey. Corrections for multiple testing were carried out within each variable.

For the assessment of adherence and its risk factors, a significant main effect was obtained for profession, F (2, 1678) = 129.48, $p < .001$. A Bonferroni multiple comparison test at the 5% level of significance showed that all three professional groups were significantly different from each other. Nurses reported significantly greater use of these interventions than doctors and pharmacists. Doctors also reported significantly greater use of these interventions than pharmacists, $p < .05$ (please see Table 5.14 for descriptive statistics). There was also a significant main effect of nation on reported use of interventions for the assessment of adherence and its risk factors, F (9, 1678) = 4.99, $p < .001$. England, Portugal and the Netherlands showed greater use of these interventions and French healthcare professionals showed the lowest use of assessment interventions.

For interventions focused on providing information for patients or carers, there was a significant main effect of profession on healthcare professionals' reported use, F (2, 1990) = 62.36, p < .001. A Bonferroni multiple comparison test indicated that doctors reported significantly more frequent use of these interventions than nurses or pharmacists, and nurses used the interventions significantly more often than pharmacists, p < .05. A significant main effect of nation was also determined, F (9, 1990) = 14.06, p < .001. Again, healthcare professionals in England, the Netherlands and Portugal reported more frequent use of these interventions. Austrian healthcare professionals reported the lowest use of this category of intervention. Descriptive statistics are shown in Table 5.14.

The ANOVA conducted on the total use of interventions regarding talking with patients about their medications revealed a significant main effect of profession, F (2, 547) = 40.83, p < .001. A Bonferroni multiple comparison test showed that nurses reported significantly more use of these interventions than doctors and pharmacists, and doctors reported significantly greater use than pharmacists, p < .05. There was also a significant main effect of nation, F (5, 547) = 4.41, p < .001. More use of these interventions was reported by healthcare professionals in Portugal and the Netherlands, and the least use was reported by Belgium. Descriptive statistics are presented in Table 5.14.

For healthcare professionals' reported use of practical strategies to make medication taking easier, a significant main effect of profession was determined, F (2, 1249) = 86.34, p < .001. A Bonferroni multiple comparison test showed that doctors reported significantly greater use of these interventions than nurses and pharmacists, and nurses reported significantly more use than pharmacists, p < .05. A significant main effect of nation also emerged, F (8, 1249) = 7.19, p < .001. Use of these interventions was highest in England, the Netherlands and Portugal and lowest in Austria and Switzerland. Descriptive statistics are reported in Table 5.14.

For the final category of interventions, focused on involving others, and other services, to support adherence, a significant main effect of profession was found, F (2, 1408) = 63.85, p < .001. A Bonferroni multiple comparison test revealed that nurses reported significantly greater use of these interventions than doctors and pharmacists, p < .05. Further, the mean total reported use of these interventions by doctors was significantly higher than the mean total use by pharmacists, p < .05. A significant main effect of nation was also observed for this outcome, F (9, 1408) = 26.55, p < .001. Healthcare professionals in Poland reported the highest use of these interventions, and Austria, Germany and Switzerland the least. Descriptive statistics are presented in Table 5.14.

Table 5.14. Descriptive statistics for healthcare professionals' total ratings for use of adherence-enhancing interventions and perceived barriers to the use of adherence-enhancing interventions

Profession/nation	N	Mean total rating	Standard deviation
Assessment of adherence and its risk factors Minimum possible score = 8 ; maximum possible score = 40			
Overall sample	1690	19.00	4.79
Doctors	642	19.59	4.28
Pharmacists	463	16.25	4.26
Nurses	585	20.52	4.83
Austria	314	18.74	4.63
Belgium	125	18.96	3.88
England	230	20.23	4.73
France	83	17.94	4.03
Germany	138	18.22	4.90
Hungary	203	19.53	5.00
Netherlands	67	19.01	4.31
Poland	283	19.29	5.62
Portugal	35	19.74	4.17
Switzerland	212	17.93	4.26
Providing information for patients/carers Minimum possible score = 9 ; maximum possible score = 45			
Overall sample	2002	28.90	5.64
Doctors	656	30.40	4.90
Pharmacists	704	27.67	5.12
Nurses	642	28.71	6.48
Austria	362	27.66	6.25
Belgium	178	28.15	4.53
England	251	31.24	5.34
France	92	29.02	5.18
Germany	197	28.96	5.19
Hungary	228	29.47	5.24
Netherlands	76	30.36	4.02
Poland	318	28.85	6.47
Portugal	38	29.87	4.63
Switzerland	262	27.79	5.16

Talking with patients about their medications Minimum possible score = 18 ; maximum possible score = 90			
Overall sample	555	55.87	11.32
Doctors	172	56.15	9.16
Pharmacists	175	50.61	10.99
Nurses	208	60.07	11.44
Austria	-	-	-
Belgium	89	52.72	10.14
England	183	57.33	10.66
France	69	53.80	10.53
Germany		-	-
Hungary		-	-
Netherlands	51	57.25	10.34
Poland		-	-
Portugal	19	59.95	9.48
Switzerland	144	55.93	13.16
Practical strategies to make medication taking easier Minimum possible score = 11 ; maximum possible score = 55			
Overall sample	1260	30.72	7.52
Doctors	532	33.29	6.12
Pharmacists	358	27.08	6.50
Nurses	370	30.54	8.71
Austria	206	30.89	7.22
Belgium	98	29.88	7.79
England	210	31.53	6.76
France	68	31.01	7.02
Germany	107	30.77	6.78
Hungary	142	32.69	8.31
Netherlands	58	31.67	5.12
Poland	180	31.31	8.36
Portugal		-	-
Switzerland	191	27.61	7.44
Involving others, and other services, to support adherence Minimum possible score = 4 ; maximum possible score = 20			
Overall sample	1420	7.47	2.79
Doctors	551	7.55	2.69

Pharmacists	415	6.32	2.18
Nurses	454	8.44	3.02
Austria	244	6.45	2.33
Belgium	121	7.36	2.33
England	203	7.77	2.42
France	68	7.82	2.44
Germany	127	6.27	2.04
Hungary	173	7.71	3.02
Netherlands	61	6.90	2.20
Poland	218	9.60	3.26
Portugal	23	8.65	2.53
Switzerland	182	6.58	2.37
Perceived barriers to the use of adherence-enhancing interventions Minimum possible score = 13 ; maximum possible score = 52			
Overall sample	1097	31.51	8.39
Doctors	382	31.55	7.65
Pharmacists	382	33.14	8.03
Nurses	333	29.59	9.19
Austria	144	31.97	8.09
Belgium	97	30.16	6.17
England	152	29.62	9.19
France	66	31.06	9.11
Germany	93	32.73	7.54
Hungary	116	33.80	8.47
Netherlands	45	27.18	6.43
Poland	200	34.66	8.49
Portugal	19	34.11	7.99
Switzerland	165	28.59	7.51

Note. Missing data result from omitted items within the online surveys; total scores could not be calculated for sections with missing items.

Analysis of variance: Interaction effects

Data were not collected from nurses in France or Germany, as the items within the survey were not relevant to the roles of nurses in these nations. A further series of ANOVAs was therefore necessary to explore the effects of interactions between profession and nation on total ratings for healthcare professionals' use of adherence-enhancing interventions, excluding all data from France and Germany. The results of these 3 x 8 between-subjects analyses of variance are presented below.

For the category of interventions pertaining to the assessment of adherence and its risk factors, a significant main effect of profession was determined, F (2, 1445) = 8.98, p < .01. There was, however, no significant main effect of nation, F (7, 1445) = .62, p > .05. A significant interaction between profession and nation emerged, F (14, 1445) = 7.73, p < .001. Pharmacists in England, the Netherlands and Portugal reported more use of these interventions than pharmacists from other countries. Nurses in Austria and Switzerland reported less use of these interventions that nurses in other countries.

There were no significant main effects of profession, F (2, 1689) = 1.35, p > .05, or nation, F (7, 1689) = 1.30, p > .05, on healthcare professionals' reported use of interventions centred on the provision of information for patients and carers. However, a significant profession x nation interaction was found, F (14, 1689) = 8.83, p < .001. Nurses in England reported much higher, and nurses in Austria much lower, use of these interventions than nurses in other nations. Pharmacists in the Netherlands and Portugal reported more frequent use of these interventions, and pharmacists in Poland and Switzerland less frequent use of these interventions.

For the use of interventions focused on talking with patients about their medications, a significant main effect of profession was determined, F (2, 471) = 7.80, p < .05. There was no significant main effect of nation, F (4, 471) = 2.03, p > .05. However, a significant profession x nation interaction effect was found, F (8, 471) = 2.52, p < .05. Nurses in the Netherlands reported higher use in this category than nurses in other countries. Pharmacists in Belgium and Switzerland reported lower use of interventions in this category.

A similar pattern of findings was determined for healthcare professionals' use of practical strategies to make medication taking easier. A significant main effect of profession was found, F (2, 1064) = 10.50, p <.01, but there was no significant main effect of nation, F (6, 1064) = 1.42, p > .05. A significant interaction effect was found, F (14, 1064) = 4.18, p < .001. Doctors in England, the Netherlands and Switzerland reported lower use of these interventions than doctors in other nations. Nurses and pharmacists in England and the Netherlands had higher use of interventions in this category than nurses elsewhere.

For the final category of interventions, focused on involving others and other services to support adherence, significant main effects were found for profession, F (2, 1201) = 8.19, p < .01, and for nation, F (7, 1201) = 6.95, p < .01. Healthcare professionals in Portugal and Poland reported more frequent use of interventions than healthcare professionals in other nations. A significant profession x nation interaction effect was also shown, F (14, 1201) = 3.44, p < .001. Pharmacists in Poland reported much lower use of these interventions than Polish doctors and nurse that completed the survey.

It was noted, however, that the small sample size for Portugal (N = 53) was problematic in terms of drawing inferences from the observed interactions. The analyses exploring potential interactions

between profession and nation were therefore repeated, excluding the Portuguese data in addition to the data from France and Germany. The results of these 3 x 7 ANOVAs are reported below.

For the category of interventions focused on the assessment of adherence and its risk factors, there was a significant main effect of profession, F (2, 1413) = 9.26, p < .01, but no significant main effect of nation, F (6, 1413) = .54, p > .05. A significant profession x nation interaction emerged, F (12, 1413) = 8.97, p < .001. Pharmacists in England, the Netherlands and Switzerland reported more use of these interventions than pharmacists in other countries. Nurses in Austria and Switzerland recounted less use of these interventions that in other nations.

No significant main effects were found for profession, F (2, 1654) = 1.52, p < .01, or nation, F (6, 1654) = 1.28, p > .05, for the use of interventions centred on the provision of information to patients and carers. However, a highly significant profession x nation interaction was found, F (12, 1654) = 10.06, p < .001. Nurses in England, doctors in Poland, and pharmacists in the Netherlands reported much higher use of interventions in this category than their respective professions in other countries.

A significant main effect of profession was determined for the use of interventions focused on talking with patients about their medications, F (2, 455) = 13.38, p < .01, but there was no significant main effect of nation, F (3, 455) = 1.92, p > .05. A significant profession x nation interaction was found, F (6, 455) = 3.04, p < .01. [Insert analyses probing interaction here]. This pattern of findings was repeated for healthcare professionals' use of practical strategies to make medication taking easier. A significant main effect of profession was determined, F (2, 1064) = 10.50, p < .01, but there was no significant main effect of nation, F (6, 1064) = 1.42, p > .05. A highly significant profession x nation interaction emerged for this outcome, F (12, 1064) = 4.18, p < .001. Nurses in the Netherlands reported more frequent use and pharmacists in Belgium less frequent use of these interventions than nurses and pharmacists in other countries.

For the use of interventions involving others and other services to support adherence, there were significant main effects of profession, F (2, 1181) = 12.64, p < .01, and nation, F (6, 1181) = 6.99, p < .01. A significant profession x nation interaction also emerged, F (12, 1181) = 3.88, p < .001. Pharmacists in England and the Netherlands reported more frequent use of this category of interventions than pharmacists in other nations.

The final analysis within this series explored the potential interaction of profession and nation on healthcare professionals' perceived barriers to the use of adherence-enhancing interventions. Although significant main effects were found for profession, F (2, 898) = 13.28, p < .001, and nation, F (6, 898) = 13.19, p < .001, there was no significant interaction effect, F (12, 898) = 1.03, p > .05. Nurses and doctors in Poland reported much higher use of these interventions than healthcare professionals elsewhere.

Perceived barriers to the use of adherence-enhancing interventions

Structure of analysis

The analysis of healthcare professionals' perceived barriers to the use of interventions for adherence followed the same structure as the analysis for healthcare professionals' use of adherence-enhancing interventions.

Analysis of variance: Main effects

A 3 x 10 between-subjects ANOVA conducted for healthcare professionals' perceived barriers to the use of adherence-enhancing interventions showed a significant main effect of profession, F (2, 1085) = 24.90, p < .001. A Bonferroni multiple comparison test revealed that pharmacists reported significantly greater barriers to implementing adherence-enhancing interventions than doctors and nurses, and doctors reported significantly greater barriers than nurses, p < .05. A significant main effect of nation was also found, F (9, 1085) = 11.97, p < .001. Healthcare professionals in Hungary, Portugal and Poland reported more barriers and healthcare professionals in the Netherlands and Switzerland reported fewer barriers to intervention than healthcare professionals in other countries. Descriptive statistics can be found in Table 5.10.

Analysis of variance: Interaction effects

The analysis conducted on healthcare professionals' perceived barriers to the use of adherence-enhancing interventions, excluding data from France and Germany, showed significant main effects of profession, F (2, 914) = 6.82, p < .01, and nation, F (7, 914) = 11.76, p < .001. There was no significant interaction between these variables on total rating for perceived barriers, F (14, 914) = 1.01, p > .05. Healthcare professionals in Hungary, Portugal and Poland reported the most barriers to intervention. Nurses reported fewer barriers than doctors and pharmacists.

Further analysis explored the potential interaction of profession and nation on healthcare professionals' perceived barriers to the use of adherence-enhancing interventions, excluding data from France, Germany, and Portugal. Although significant main effects were found for profession, F (2, 898) = 13.28, p < .001, and nation, F (6, 898) = 13.19, p < .001, there was no significant interaction effect, F (12, 898) = 1.03, p > .05. Overall, nurses reported lower levels of barriers than doctors and pharmacists. Healthcare professionals in Poland and Hungary reported the most barriers and healthcare professionals in the Netherlands the lowest number of barriers to intervention.

Supplementary analyses

The extent to which barriers to the use of adherence-enhancing interventions were perceived was compared between healthcare professionals who reported using the primary outcome intervention and those who reported that they never asked patients about missed doses of medication. A between-samples t-test indicated that those healthcare professionals who reported using the primary outcome intervention perceived significantly less barriers to the use of adherence-enhancing

interventions (M = 31.33, SD = 8.35) than those who reported that they never asked patients about missed doses (M = 35.46, SD = 8.52), t (1081) = -3.28, p < .01.

Beliefs about patients' adherence to medication

Internal reliability of measure

Cronbach's alpha indicated that the internal reliability of items assessing healthcare professionals' beliefs about patients' adherence to medication was poor. It was therefore inappropriate to calculate total scores for this measure.

Perceptions of the extent of non-adherence

To assess healthcare professionals' optimistic bias for perceptions of their own patients' adherence, their estimates for the percentages of their own patients who do not initiate prescribed medication, adhere to prescribed medication, and persist with prescribed medication for one year were compared with their estimates for patients in general within their nation, for the same aspects of adherence. Specifically, respondents were asked to rate the percentages of patients with a chronic illness or condition who do not initiate prescribed medication; who initiate prescribed medication and do take their medicines as prescribed; and who initiate prescribed medication and persist with the medication, for their own patients and for all patients within their nation. The percentages for each response category for healthcare professionals' own patients and patients in general are provided for the overall sample and for each profession within Table 5.15. A series of tests were conducted to determine whether there were significant differences between the healthcare professionals' ratings for their own patients and those for patients in general, for each aspect of adherence. For non-initiation, a nonparametric sign test showed that healthcare professionals' ratings for their own patients were highly significantly lower than those for patients in general, p < .001, suggesting optimistic bias for healthcare professionals' perceptions of their own patients' non-initiation. For all pairs of responses to the items on non-initiation, 788 ratings for healthcare professionals' own patients were lower than those for patients in general, while 201 ratings were higher. A Wilcoxon signed rank test for the difference in median ratings for healthcare professionals' own patients and patients in general confirmed that this difference was significant, p < .001.

These tests were also conducted for healthcare professionals' estimates of the percentage of patients who do take their medicines as prescribed, both within their own patients and in general in their nation. The sign test indicated that ratings for healthcare professionals' own patients' adherence were highly significantly lower than ratings for the adherence of patients in their nation in general, p < .001. Of all pairs of responses, 894 ratings for healthcare professionals' own patients were lower than ratings for patients in general, while 788 were higher. A Wilcoxon signed rank test confirmed that the median ratings for healthcare professionals' own patients was significantly lower than that for patients in general, p < .001.

For healthcare professionals' estimates of patients' persistence for one year, a sign test indicated that ratings were significantly higher for their own patients than for patients in their nation in general,

$p < .001$. Of all pairs of ratings, 299 ratings were lower for healthcare professionals' own patients, relative to patients in general, while 819 were higher, indicating that optimistic bias is also present in healthcare professionals' estimates of patients' persistence with prescribed medication. A Wilcoxon signed rank test confirmed that the median rating for healthcare professionals' own patients was significantly higher than the median rating for patients in their nation in general, $p < .001$.

To explore differences in optimistic bias between the three professional groups, a series of Kruskal Wallis one-way ANOVAs were conducted. Initially, difference scores were computed for each aspect of adherence by subtracting each healthcare professional's rating for patients in general from their rating for their own patients; both assessed on the same five point scale. These difference scores formed the outcome variable for the ANOVAs. For non-initiation, negative difference scores indicated optimistic bias, while positive scores reflected the perception that non-initiation was greater in the healthcare professionals' own patients than patients in general. For adherence and persistence, positive scores indicated optimistic bias. The ANOVA conducted for the non-initiation difference score showed a significant difference between the professional groups, $p < .001$. Pairwise comparisons using the Mann-Whitney test indicated that pharmacists reported significantly more positive difference scores, and therefore less optimistic bias, than doctors and nurses on this variable. There was no significant difference between the difference scores of doctors and nurses.

For healthcare professionals' difference scores for patients' adherence to prescribed medication, a significant difference between the professions emerged, $p < .001$. Mann-Whitney tests revealed that the difference scores reported by nurses were significantly more positive than those of doctors and pharmacists, $p < .001$, indicating significantly more optimistic bias from nurses. Pharmacists' scores were also significantly more positive than those of the doctors, $p < .001$. A significant difference between professions was also determined for difference scores for patients' one year persistence with prescribed medication, $p < .001$. In this case, doctors' difference scores were significantly more positive than those of pharmacists, $p < .001$, and nurses, $p < .05$, suggesting that doctors exhibit more optimistic bias for their own patients' persistence with prescribed medication than either pharmacists or nurses. There was no significant difference between the level of optimistic bias shown by pharmacists and nurses, $p > .05$.

A series of Mann Whitney tests were conducted to explore differences in the extent of healthcare professionals' optimistic bias, operationalised as differences between ratings of their own patients' adherence to prescribed medication relative to the adherence of patients in general within their nation, between those who reported using the primary outcome intervention and those who reported never using this intervention. Results indicated that there were no significant differences in optimistic bias between healthcare professionals who stated that they do ask patients about missed doses of medication and those who reported that they never ask patients about missed doses, for any of the pairs of items.

Table 5.15. Perceptions of the extent of medication non-adherence (percentages)

What percentage of ALL PATIENTS/PATIENTS THAT YOU SEE with a chronic condition, do you think do NOT initiate prescribed medication (that is, patients who do NOT take any of their prescribed medication)?						
Group	**Target**	**0-15%**	**16-35%**	**36-65%**	**66-85%**	**86-100%**
Overall	Own patients	67.80 *(N = 1468)*	24.03 *(N = 691)*	6.22 *(N = 179)*	1.39 *(N = 40)*	0.56 *(N = 16)*
	Average	49.03 *(N = 1468)*	37.71 *(N = 1129)*	11.46 *(N = 343)*	1.54 *(N = 46)*	0.27 *(N = 8)*
Doctors	Own patients	68.23 *(N = 537)*	25.29 *(N = 199)*	4.45 *(N = 35)*	1.40 *(N = 11)*	0.64 *(N = 5)*
	Average	45.17 *(N = 365)*	42.45 *(N = 343)*	11.51 *(N = 93)*	0.87 *(N = 7)*	0 (N=0)
Pharmacists	Own patients	71.49 *(N = 810)*	22.15 *(N = 251)*	5.21 *(N = 59)*	0.79 *(N = 9)*	0.35 *(N = 4)*
	Average	57.80 *(N = 693)*	33.53 *(N = 402)*	7.59 *(N = 91)*	0.92 *(N = 11)*	0.17 (N = 2)
Nurses	Own patients	63.08 *(N = 603)*	25.21 *(N = 241)*	8.89 *(N = 85)*	2.09 *(N = 20)*	0.73 *(N = 7)*
	Average	41.54 *(N = 410)*	38.91 *(N = 384)*	16.11 *(N = 159)*	2.84 *(N = 28)*	0.61 (N = 6)

What percentage of ALL PATIENTS/PATIENTS THAT YOU SEE with a chronic condition, and who initiate their prescribed medication DO take their medication as prescribed?						
Group	**Target**	**0-15%**	**16-35%**	**36-65%**	**66-85%**	**86-100%**
Overall	Own patients	21.93 *(N = 630)*	13.23 *(N = 380)*	22.42 *(N = 644)*	29.41 *(N = 845)*	13.02 *(N = 374)*
	Average	2.64 *(N = 79)*	16.01 *(N = 479)*	38.40 *(N = 1149)*	36.10 *(N = 1080)*	6.85 *(N = 205)*
Doctors	Own patients	32.74 *(N = 258)*	14.09 *(N = 111)*	18.27 *(N = 144)*	23.98 *(N = 189)*	10.91 *(N = 86)*
	Average	2.73 *(N = 22)*	17.76 *(N = 143)*	39.01 *(N = 314)*	33.79 *(N = 272)*	6.71 *(N = 54)*
Pharmacists	Own patients	21.98 *(N = 249)*	12.62 *(N = 143)*	24.10 *(N = 273)*	29.74 *(N =337)*	11.56 *(N = 131)*
	Average	1.67 *(N = 20)*	14.33 *(N = 172)*	41.67 *(N = 500)*	36.08 *(N = 433)*	6.25 *(N = 75)*
Nurses	Own patients	12.92 *(N = 123)*	13.24 *(N = 126)*	23.84 *(N = 227)*	33.51 *(N = 319)*	16.49 *(N = 157)*
	Average	3.75 *(N = 37)*	16.62 *(N = 164)*	33.94 *(N = 335)*	37.99 *(N = 375)*	7.70 *(N = 76)*
What percentage of ALL PATIENTS/PATIENTS THAT YOU SEE with a chronic condition, and who initiate their prescribed medication DO persist with their medication for 1 year?						

Group	Target	0-15%	16-35%	36-65%	66-85%	86-100%
Overall	Own patients	2.68 *(N = 77)*	12.28 *(N = 353)*	32.25 *(N = 927)*	38.59 *(N = 1109)*	14.20 *(N = 408)*
	Average	3.25 *(N = 97)*	16.31 *(N = 487)*	38.46 *(N = 1148)*	34.47 *(N = 1029)*	7.50 *(N = 224)*
Doctors	Own patients	1.91 *(N = 15)*	13.78 *(N = 108)*	32.78 *(N = 257)*	39.41 *(N = 309)*	12.12 *(N = 95)*
	Average	3.49 *(N = 28)*	20.45 *(N = 164)*	38.78 *(N = 311)*	32.17 *(N = 258)*	5.11 *(N = 41)*
Pharmacists	Own patients	1.68 *(N = 19)*	10.41 *(N = 118)*	35.98 *(N = 408)*	40.56 *(N = 460)*	11.38 *(N = 129)*
	Average	1.92 *(N = 23)*	13.17 *(N = 158)*	42.08 *(N = 505)*	35.75 *(N = 429)*	7.08 *(N = 85)*
Nurses	Own patients	4.50 *(N = 43)*	13.28 *(N = 127)*	27.41 *(N = 262)*	35.56 *(N = 340)*	19.25 *(N = 184)*
	Average	4.68 *(N = 46)*	16.79 *(N = 165)*	33.77 *(N = 332)*	34.79 *(N = 342)*	9.97 *(N = 98)*

Note. Response scale: 1 = 0-15%; 2 = 16-35%; 3 = 36-65%; 4 = 66-85%; 5 = 86-100%

5.6.4 Discussion

5.6.4.1 Main findings and conclusions

Healthcare professionals in Europe are limited in the extent to which they intervene to assist patients with long term conditions with medication adherence. Within intervention categories, mean total scores are around or below the mid-point for 'assessment of adherence', 'practical strategies to make medication taking easier', and 'involving others to support adherence'. The categories 'providing information for patients/carers' and 'talking with patients about their medications' (of which giving patients the opportunity to ask questions is highly rated) both score slightly above the mid-point of the total scale, suggesting these categories of intervention are practised somewhat more frequently.

The analysis of the primary outcome, and of the 'assessment of adherence' category as a whole, generates concern about the extent to which healthcare professionals seek to identify medication non-adherence in routine clinical practice. Participants in the survey were asked to answer each question only if the specific item was relevant to their role. Thus participants for whom the item was relevant to their role, and so answered the question, could potentially have asked all patients about missed doses of prescribed medication. In fact, about half of the healthcare professionals in the survey ask patients with long term conditions whether they have missed any doses of their medication on a regular basis, a question identified as a key method for healthcare professionals to assess adherence and so support patients with medicines (http://publications.nice.org.uk/medicines-adherence-cg76/guidance#supporting-adherence). However, the finding that healthcare professionals who report that they have had some element of training in medication adherence are more likely to ask this key question, indicates that healthcare professional behaviour may perhaps be amenable to change in this regard.

Robust differences are found in the extent to which doctors, pharmacists and nurses report that they manage and support patients with medication adherence. For the primary outcome, and all five categories of adherence intervention, pharmacists persistently report that they intervene less than the other two professions to support patients with medicines. In three instances of five, nurses reported more intervention than doctors to assist patients with prescribed medicines.

Several factors may hinder pharmacists from intervening to the same extent as nurses or doctors. Pharmacists report significantly more barriers that prevent them from using adherence-enhancing interventions. In particular, pharmacists report less access to evidence-based information to support such practice, and report more difficulties with continuity of care and integration with other healthcare providers than doctors and nurses. With doctors, pharmacists also report that payment incentives and inadequate resources are barriers to action, more so than nurses. It is possible that the physical environment and role of many pharmacists in community and primary care settings may hinder their

ability to assist patients to the same extent as nurses and doctors. However, in this survey pharmacists report no less time to spend talking with patients about their use of medications than doctors, though both groups report that they typically have less time to spend with individual patients than nurses. It is also unlikely that access to training inhibited pharmacists from intervening to support patients with medication adherence: pharmacists in this study reported receiving more adherence training than either nurses or doctors.

The differences between professions in the extent to which they report that their day to day practice includes supporting patients with long term conditions with medicines use is cause for concern. Within the primary care team, pharmacists have particular expertise and training in pharmaceuticals, yet this does not appear to translate into a lead role in supporting patients with medicines use within routine practice. The evidence from this survey suggests that lack of integration of the pharmacy and pharmacist with other healthcare professionals and providers, and appropriate resource and recompense for service provision, are the more likely barriers to pharmacist involvement in medicines optimisation.

No country effects were found for the primary outcome examining responses to the question specifically concerning whether healthcare professionals ask patients if they have missed any doses of their medication. For the interventions section of the survey as a whole, differences between countries are found in the extent to which healthcare professionals in primary care settings intervene to support patients with medicines use. Healthcare professionals in England, the Netherlands and Portugal report more activity to support patients with medicines use for three of the five categories of intervention (assessment of adherence, providing information for patients/carers and practical strategies to make medication taking easier) than healthcare professionals in the other countries. Healthcare professionals in the Netherlands and Portugal, but not England, also report more activity in the talking with patients about medications category. The pattern of findings is different for the involving others and other services to support adherence category, for which Polish healthcare professionals report more activity than healthcare professionals in other countries. Interaction effects between profession and countries are reported above for completeness but should be interpreted with caution in the absence of a main effect of country in the majority of these analyses.

The relatively small sample of healthcare professionals in Portugal cautions against over interpretation of these findings regarding Portugal. Results from England, the Netherlands and Poland however, are supported by much larger samples. Future research might usefully consider whether aspects of service provision, training or healthcare culture contribute to these differences in clinical behaviour.

A clear theme regarding the use of adherence-enhancing interventions by healthcare professionals is the low reported use of technology and other resources to support patients with medicines use in routine practice. Resource-intensive approaches are utilised less than resource-light approaches. Thus, blood or

urine screens and electronic monitoring to assess medication adherence, DVDs, video or computer resources for information provision, and reminder systems such as text messaging, mobile alarms, reminder charts and diaries are used less to support medication adherence than non-technological, simple approaches, such as information sharing and talking with patients about their medicines use. Unfortunately from this survey, we are unable to determine whether this is due to the lack of availability of such resources or a preference by healthcare professionals for less technologically-driven approaches. However, we do know that healthcare professionals who report use of these interventions, and thus respond to the questions about perceived effectiveness of the intervention items, are in general more likely to report that they 'don't know' how effective the interventions are than participants responding to other items.

Healthcare professionals in the study report that, of the interventions they use, provision of information to patients and talking with patients about their medicines use, are more effective than other ways of intervening, in their view. However, the sample does not strongly endorse the effectiveness of many of the interventions they use; just 10 of the 50 interventions have a modal response of 'extremely' effective. It is possible then that healthcare professionals struggle to get feedback on the utility and effectiveness of their own actions to support patients with medication adherence. If so, healthcare professionals may find it difficult to reflect upon, learn from and adapt their own practice to support medicines use.

Previous research has shown that doctors and nurse are inaccurate in their estimates of the incidence of non-adherence and their estimates are less accurate than patients' own estimates.[2] The current study adds evidence that healthcare professionals experience optimistic bias[3] in their perceptions of medication non-adherence, perceiving that their own patients are 'better' at adhering than the general population. Usually optimistic bias is reported for self attributes: people perceive, on average, that their own futures are going to be better than others, and that they are exposed to fewer risk factors than other people and that they have more positive personal attributes than other people. This is the first study we are of that has demonstrated that optimistic bias in a healthcare professional sample extends to perceptions of the healthcare professionals' patients versus patients in general. Theories of optimistic bias tend to report that it is a self-serving bias, supported by biases in cognitive mechanisms, serving a self-enhancing self-protective function. For healthcare professionals in the current study, it may be the case that the self-enhancement is served by extending this cognitive bias about oneself to include perceptions about 'my patients'. The potential impact of this bias on healthcare professional behaviour concerning medication adherence support for patients is unclear.

5.6.4.2 Strengths and limitations

In some countries, and for some professions, participant recruitment did not approach the target sample size. Recruitment of general practitioners to the study was a particular problem for some countries. In

England, for example, recruitments of pharmacists and nurses to the study was steady and straightforward, with the combined approach to participant recruitment. Professional bodies and regulators for GPs however, were less able to assist with recruitment. Further, regional support for the involvement of GPs in research studies was limited to assisting studies funded by National rather than European funded research studies. Other countries, for example, France, Belgium and Switzerland, have a culture of payment to GPs for participation in surveys like this, which was not part of the protocol for this study. Some potential participants also reported 'questionnaire fatigue', and reported that they receive a multitude of invitations to participate in surveys. Some countries experienced difficulties in recruiting participants to the study across professions, despite best efforts to increase participation through a number of approaches to recruitment, such as direct mailing, social media, etc. For some analyses, countries had to be excluded due to low sample sizes. Whilst online surveys have many advantages, participant recruitment can be variable. These practical difficulties should be taken into account by future researchers undertaking online surveys of healthcare professionals.

Two countries, France and Germany, did not plan to collect data for nurses working in a primary care setting. Survey partners in those countries reported that the study topic was not so relevant to the role of nurses in those nations. For some analyses, the absence of a nurse sample for all countries meant that interaction effects could not be reported unless the whole dataset for these specific countries was excluded. Further, some participants started but did not complete all sections of the survey so producing missing values for some parts of the survey.

The study focused on the beliefs and behaviours of healthcare professionals working primarily in a primary care setting. This study does not tell us about beliefs and behaviours to support medication adherence by those working in secondary care health services, nor is it possible to determine the extent to which the results of the present study may be generalizable to other settings. The survey concerns self-report by healthcare professionals of the interventions they undertake to manage and support patients with medication adherence. We have no objective evidence to support these self-reports. Equally, we have no information about the patient experience of support with medicines taking by the professionals participating in the study.

Furthermore, healthcare professionals completing this survey chose whether to participate or not. This self-selected sample may be more interested in medicines and medicines use than the healthcare professional population at large. If so, this study may overestimate the proportion of healthcare professionals who use adherence-enhancing interventions.

To our knowledge however, this study is the largest survey of European health care professionals' medication adherence perceptions, beliefs and behaviours. Keeping in mind the caveats above, the results add to our understanding of how health care professionals perceive medication non-adherence.

By gaining a deeper understanding of health care professionals' perceptions and behaviour with regards to non-adherence in their patients, researchers will be able to design educational interventions and training for health care professionals that is evidence-based and targeted at the training needs of health care professionals.

This study also provides information on the interventions most frequently used by healthcare professionals and their perceptions of which interventions are most effective in managing non-adherence. This provides evidence-based knowledge of interventions which health care professionals have found to be effective at improving patient adherence. Healthcare professionals can use this information as a guide when making a decision about which interventions to make use of or to recommend to patients in order to improve adherence. Information on which interventions are reported to be less effective could help to channel the efforts of researchers towards finding ways to improve those interventions.

The international nature of this study provides a comprehensive data set which enables analysis of variability observed in healthcare professionals' beliefs and behaviours across 10 European nations. It is anticipated that this knowledge of the level of variability between professions in adherence-supporting behaviour, may provide a basis within each country for promoting routine and continuous efforts to educate and modify the behaviour of healthcare professionals in order to enable them to fulfil their roles in supporting patients with medicine taking.

5.6.4.3 Implications and recommendations

This study shows that there is plenty of scope for primary care healthcare professionals to increase the frequency with which they provide support to patients with long term conditions prescribed medication to support medication adherence. Previous studies of clinical behaviour change for other aspects of clinical practice have used social cognitive theory to understand the determinants of healthcare professional behaviour and as the basis for the design of interventions to change the clinical practice of healthcare professionals.[19-21] Future research might adopt the same approach in the development of interventions to improve the uptake of medication adherence guidelines by healthcare professionals.

We recommend that a quality standard for medication adherence support for people with long term conditions should be introduced for primary care settings in Europe with the following quality statement: people prescribed medication(s) for long term conditions receive an assessment that identifies the extent of non-adherence to medication. The recommended quality measure is the proportion of patients prescribed medication who are asked whether they have missed any doses of their medication for a recent timeframe during their most recent consultation (numerator – the number of people with a long term condition prescribed medication who were asked whether they have missed any doses of their

medication during their most recent consultation; denominator - the number of all patients with a long term condition prescribed medication). This survey serves as one source of evidence against which performance for this quality standard can be benchmarked. The aim of this quality standard is to make medication adherence assessment a regular and routine part of primary health care, and so provide a basis for healthcare professionals to support patients reporting non-adherence with medicines use when necessary.

Further study is needed to investigate ways in which healthcare professionals can receive feedback about the impact and effectiveness of specific adherence-enhancing interventions used in routine clinical practice, to support healthcare professionals in reflecting upon and improving their practice. Options include patient satisfaction reporting, peer and self-assessment methods and more standardised outcome measurement.

Finally, this study provides evidence to support a strong case for educators to reflect on the nature and extent of the education and training provided to healthcare professionals for managing and supporting patients with medication adherence. Nilsen et al caution that the habitual nature of much clinical practice may lead to resilience to attempts to modify clinical practice.[22] The educational framework presented in Chapter 8 is recommended as a basis for adherence education for pre-registration training and for continuing professional development for healthcare professionals.

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5.7 Systematic review of clinical practice guidelines for the improvement of medication adherence

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5.7.1 Summary

This review evaluated the currently available clinical practice guidelines available to help health care providers address and manage medication adherence issues with their patients. We found that few guidelines are available, and the level of detail in recommendations is low. These guidelines do serve as a starting point, however, for adapting or developing guidelines for use in the European Union and included in health care professional training curricula.

5.7.2. Introduction

Adherence to medications is defined as the process by which patients take their medications as prescribed. It is composed of three parts: initiation, implementation, and discontinuation.[1 2] Adherence to medications is essential for medications to be used effectively and for patients to achieve the clinical benefit from medication therapy.

Suboptimal adherence to prescribed medication regimens exists with all clinical conditions and populations, leading to poorer treatment outcomes,[3] increased risk for adverse health events, and higher utilization of health care services, hospitalizations, and health care costs.[4] The World Health Organization, in a 2003 report, declared non-adherence to medical treatment a major public health concern, particularly among patients with chronic conditions.[5]

While numerous interventions have been tested to address the problem of medication non-adherence,[6 7] very few comprehensive practice guidelines have been developed for clinicians to use when addressing medication non-adherence with patients. Of those guidelines in existence, little is known about how the guidelines were developed or whether there is consistency across guidelines with the recommendations for how to address medication non-adherence.

5.7.3. Objectives

The aim of work package 4.4 was to conduct a systematic review of national and international guidelines on the management of patient compliance and adherence to medications. We sought to answer the following research questions:

1. What national and international medication adherence guidelines exist?

2. What are the characteristics of existing national- and international-level medication adherence guidelines?
3. What processes have been used to develop medication adherence guidelines?
4. How have medication adherence guidelines been distributed?
5. Where have the reports been published?

5.7.4. Method

To meet this objective, a search strategy was developed to locate and identify clinical practice guidelines for medication adherence meeting the following criteria:

Inclusion/Exclusion criteria:

1. A publication (e.g., journal article, white paper, consensus document) outlining guidelines for addressing medication compliance, adherence, persistence, or concordance in clinical practice, healthcare systems, or research.
2. The guidelines must be national or international in scope.
3. The guidelines must deal primarily with medication adherence behavior
4. The publication's purpose must have been to develop guidelines to improve medication compliance, adherence, persistence, or concordance. Research studies or review articles that only make recommendations as a part of the conclusions will be excluded.

The search for guidelines was initiated by identifying and obtaining national and international guidelines known to the ABC Project partners. We then expanded this by sending a request out to the e-mail list of the European Society for Persistence, Adherence, and Compliance (ESPACOMP). Guidelines suggested by these experts were obtained to be reviewed for eligibility. A structured database search was then conducted in using MEDLINE (PubMed), CINAHL, EMBASE, and the Cochrane Library. The search strategies for each database are shown in Table 5.16.

Table 5.16: Database search terms

	MEDLINE:
1	Patient compliance [majr] OR treatment refusal [majr]
2	practice guideline OR position paper OR white paper OR policy document OR consensus statement OR consensus report OR consensus conference OR policy report OR policy guideline OR consensus meeting OR practice recommendation OR round table OR roundtable OR task force OR consensus guideline
3	1 and 2

	CINAHL:
1	"compliance" OR adherence OR persistence or concordance OR nonadherence OR non-

	adherence OR noncompliance OR non-compliance
2	practice guideline OR position paper OR white paper OR policy document OR consensus statement OR consensus report OR consensus conference OR policy report OR policy guideline OR consensus meeting OR practice recommendation OR round table OR roundtable OR task force OR consensus guideline
3	1 and 2

	EMBASE:
1	'Patient compliance'/exp/mj
2	'practice guideline'/exp OR 'position paper' OR 'white paper' OR 'policy document' OR 'consensus statement' OR 'consensus report' OR 'consensus conference' OR 'policy report' OR 'policy guideline' OR 'consensus meeting' OR 'practice recommendation' OR 'round table' OR 'roundtable' OR 'task force' OR 'consensus guideline'
3	1 and 2

	Cochrane Library:
1	Patient compliance [MeSH] OR treatment refusal [MeSH]
2	'practice guideline'/exp OR 'position paper' OR 'white paper' OR 'policy document' OR 'consensus statement' OR 'consensus report' OR 'consensus conference' OR 'policy report' OR 'policy guideline' OR 'consensus meeting' OR 'practice recommendation' OR 'round table' OR 'roundtable' OR 'task force' OR 'consensus guideline'
3	1 and 2

Finally, internet searches were conducted using applicable search engines (e.g., Google, Google Scholar, Yahoo, Bing) to identify any possible adherence management guidelines that had not been published in the indexed academic literature. We conducted general searches and also searches specific to results from specific countries/regions (e.g., .eu, .uk, .be, .fr, .de). We reviewed the first 100 results for general searches and the first 10 results for country/region specific searches using the following search terms:

Search terms:

1. medication adherence guidelines
2. medicine adherence guidelines
3. medicines adherence guidelines
4. medication compliance guidelines
5. medicine compliance guidelines
6. medicines compliance guidelines

7. medication adherence consensus statement
8. medicine adherence consensus statement
9. medicines adherence consensus statement
10. medication compliance consensus statement
11. medicine compliance consensus statement
12. medicines compliance consensus statement
13. medication management consensus statement
14. medicine management consensus statement
15. medicines management consensus statement
16. medication adherence white paper
17. medicine adherence white paper
18. medicines adherence white paper
19. medication compliance white paper
20. medicine compliance white paper
21. medicines compliance white paper
22. medication management white paper
23. medicine management white paper
24. medicines management white paper

Data extracted from the eligible guidelines included the citation information, year of publication, health condition of interest, how the guideline was developed, what specific recommendations were made, and whether the guideline included an algorithm for adherence management.

Since the guidelines varied greatly in the types of recommendations and the detail provided, a content analysis leading to categories of interventions was conducted for the purposes of organizing the results. The results are not presented according to a particular conceptual model, since the practice guidelines did not cite conceptual models, and there is a great deal of conceptual overlap in health behavior models, where intervention components could easily fit into more than one model.

5.7.5. Results

The initial searching in MEDLINE, CINAHL, EMBASE, and the Cochrane Library resulted in 1333 unique citations. Independent review of the titles and abstracts of each citation by two reviewers reduced this number to 140 potentially eligible citations. An additional 14 potential sources were recommended by experts, and an additional five potential unique sources from the internet searches. The full text of these 159 documents were reviewed for final eligibility, with 17 documents meeting the eligibility criteria (see Figure 5.1). The most common reason for exclusion was that the publication did

not provide practice recommendations for improving or managing medication adherence. Table 5.17 contains an overview of all guidelines retrieved.

Of the eligible guidelines, the majority originated in the United States (n=8). Three originated in Canada, two in the UK, one in Spain. Two had an international origin—one in Central and South America, and one with authors from a variety of countries. Regarding the intended scope of the guidelines, nine focused were intended for their country of origin, three were intended for an international audience, and five guidelines did not include specific information about the guideline's intended scope. The guidelines' treatment foci included HIV/AIDS,[8-11] cardiovascular disease,[12-15] contraception,[16 17] menopause,[18 19] mental health[20] or depression,[21] and asthma.[22] Two guidelines were general guidelines, and did not specify a health condition focus.[23 24]

Figure 5.1. Search flow diagram

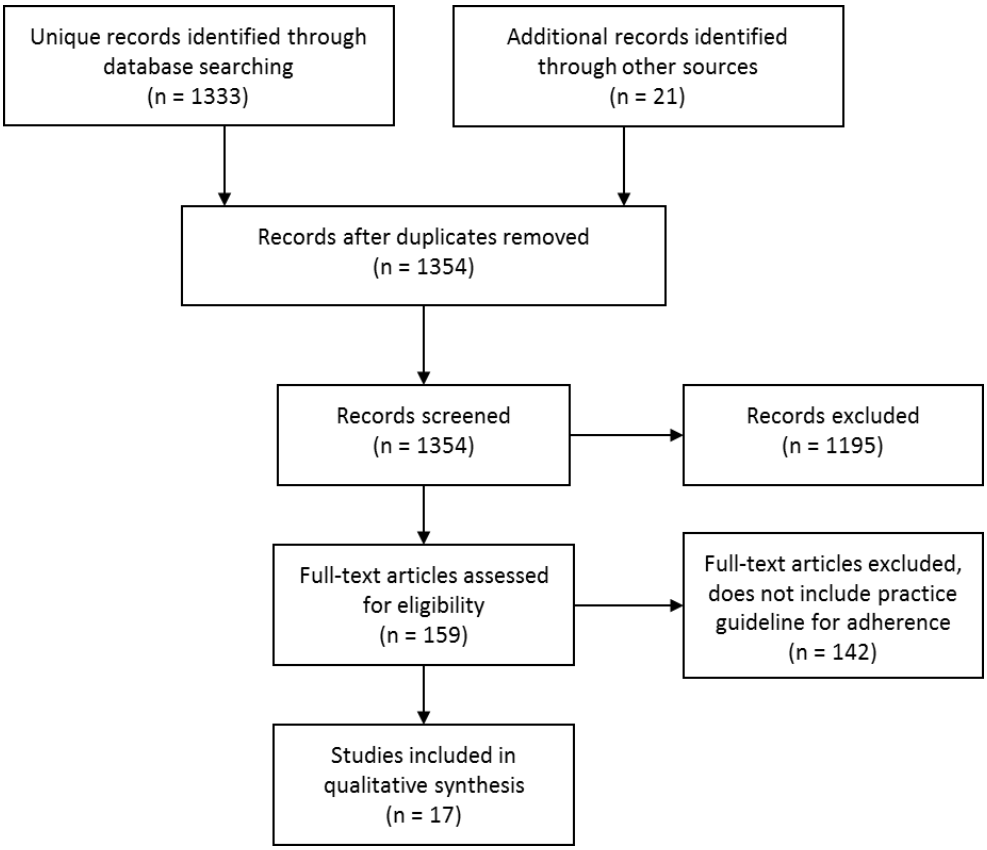

Table 5.18 reports a summary of the reported methods used to develop each guideline. Although most clearly used an expert consensus panel (n=11), reviewed existing literature (n=13), or a combination of the two, only five guidelines provided a detailed description of the methods used, including details of the literature search and the criteria for consideration, or the procedures for how the expert panel functioned to reach their final recommendations.

The initial review of included publications extracted a list of 41 types of recommendations. This initial list of recommendations was re-reviewed, merging similar recommendations under broader themes that emerged as the content of the guideline recommendations was reviewed.

Table 5.17: List of included guidelines

Primary Author	Year	Publication	Health Population Focus	Guideline Scope	Nation(s) of Origin	Sponsoring Organization
Aliotta[24]	2004	*Advances in Therapy*	not specified	unclear	USA	n/a
Benagiano[17]	1993	*British Journal of Family Planning*	Contraception	International	International	International Working Group on Enhancing Patient Compliance and Oral Contraceptive Efficacy
Canadian Hypertension Education Program[15]	2006	*Can Nurse*	Hypertension	National	Canada	Canadian Hypertension Education Program (CHEP)
Chockalingam[14]	1998	*Canadian Journal of Public Health*	Hypertension	National	Canada	Advisory Committee on Adherence to the Management of High Blood Pressure
Guilbert[16]	2008	*J Obstetrics and Gynaecoogy of Canada*	Contraception	National	Canada	Society of Obstetricians and Gynaecologists of Canada
Houston-Miller[12]	1997	*Circulation*	Cardiovascular disease	National	USA	American Heart Association Expert Panel on Compliance
Knobel[10]	2000	*Enferm Infecc Microbiol Clin*	HIV/AIDS	National	Spain	Study Group on AIDS (GESIDA) of the SEIMC, by the Spanish Society of Hospital Pharmacy (SEFH) and the National AIDS Plan (PNS), Ministry of Health (MSC)
Machtinger[11]	2007	*AIDS Reader*	HIV/AIDS	unclear	USA	n/a
Maia[19]	2007	*Maturitas*	Menopause (ERT/HRT)	International	Latin America (Central & South America)	n/a

Primary Author	Year	Publication	Health Population Focus	Guideline Scope	Nation(s) of Origin	Sponsoring Organization
National Asthma Council[22]	2005	*n/a*	Asthma	National	Australia	National Asthma Council
North American Menopause Society[18]	1998	*Menopause*	Menopause (ERT/HRT)	International	USA	North American Menopause Society
Nunes[23]	2009	*n/a*	not specified	National	UK	National Collaborating Center for Primary Care and Royal College of General Practitioners
Ockene[13]	2002	*J Am Coll Cardiol*	Cardiovascular disease	unclear	USA	American College of Cardiology
Panel on Clinical Practices for Treatment of HIV Infection[8]	2001	*HIV Clinical Trials*	HIV/AIDS	National	USA	U.S. Department of Health and Human Services; Henry J. Kaise Family Foundation
Poppa[9]	2004	*HIV Medicine*	HIV/AIDS	National (UK)	UK	British HIV Association (BHIVA) and British Association for Sexual Health and HIV (BASHH)
Trivedi[21]	2007	*CNS Spectrums*	Depression	unclear	USA	n/a
Velligan[20]	2009	*Journal of Clinical Psychiatry*	Mental health	unclear	USA	Comprehensive Neuroscience, Inc.

Table 5.18: Reported guideline development methods

Author	Year	Methods specifically described	Methods	Quality of evidence rated?
Aliotta	2004	N	methods not described	N
Benagiano	1993	N	literature review	N
Canadian Hypertension Education Program	2006	N	expert panel; literature review	Y
Chockalingam	1998	N	literature review	Y
Guilbert	2008	Y	literature review	Y
Houston-Miller	1997	N	expert panel; literature review	N
Knobel	2000	(abstract only)	expert panel	Unknown
Machtinger	2007	N	literature review	N
Maia	2007	Y	literature review; expert opinion survey (n=72)	N
National Asthma Council	2005	N	expert consensus workshop; literature review	N
North American Menopause Society	1998	Y	expert consensus conference	N
Nunes	2009	Y	literature review; expert panel	Y
Ockene	2002	N	expert panel consensus meeting; literature review	N
Panel on Clinical Practices on HIV Prevention	2001	N	expert panel	N
Poppa	2004	N	expert panel; review of meta-analyses (2) and RCTs (9)	N
Trivedi	2007	N	methods not described	N
Velligan	2009	Y	expert panel survey (n=41); literature review	N

5.7.5.1 Educational Strategies

Fourteen of the guidelines (82%) included an educational component to their recommendations. Those guidelines that provided detailed instructions about educational approaches specified the need to provide clear instructions for how patients should take their medications. Three of the guidelines (two focusing on contraceptives and one general guideline) suggest that health care providers provide instructions to patients for what to do in the case of missed doses.

Where necessary, it can be useful to provide additional education for patients who may lack the necessary insight into their condition.[20 24] In these cases, providing educational content on the consequences of non-adherence and the therapeutic benefits of effective medication adherence can help the patient to understand the need for adequate adherence, providing the necessary knowledge for establishing motivation to adhere.

5.7.5.2. Motivation/Stigma Strategies

Four guidelines addressed issues related to motivation to take medications. Three of the guidelines recommended motivational interviewing as a method for improving adherence to medications,[9 11 24] while the remaining guideline, dealing with adherence in mentally ill patients, recommended cognitive-behavioral therapy and/or patient psychoeducation.[20]

The rationale for these approaches are for the provider to develop a rapport with the patient, assess the patient's motivation to adhere and readiness to change, and then collaborating with the patient to establish goals and make behavioral changes necessary to improve medication adherence behavior.[20,24] The guidelines acknowledged that evidence supporting the effectiveness of motivational interviewing, cognitive-behavioral therapy, and patient psychoeducation is inconclusive.

5.7.5.3 Behavioral Strategies

Behavioral strategies are being increasingly recognized as an important component of intervention programs to manage and improve adherence to medications (see WP5 report). Behavioral strategies vary, but can include unit-dose packaging, medication self-monitoring, symptom or side-effect self-monitoring, reminders or other stimuli or cues to take medications, feedback, and associating medication-taking with other daily activities. Such approaches help patents to use the knowledge gained from educational approaches and apply them by actually doing things to modify behavior.

Fourteen of the guidelines (82%) included a recommendation for a behavioral strategy. The most frequent strategies recommended were simplification of the medication regimen and symptom or side effect monitoring. Each were recommended by seven guidelines (41%). Six guidelines, however, made nonspecific recommendations for "behavioral strategies" and five recommended

individually tailoring medication regimens. The lack of specificity of many guidelines makes it difficult to reach conclusions on which behavioral approaches are actually the most recommended.

5.7.5.4. Assessment

A majority of the guidelines (n=14, 82%) recommended some type of assessment of adherence or of factors relating to adherence. Nine studies (53%) recommended that health care providers should regularly assess patients' adherence to medications. Five of the nine suggested self-report measures of adherence as an option, although two of these recommended that other measures be used as well. A listing of the number of guidelines making assessment recommendations is listed in Table 5.19.

Table 5.19. Assessment recommendations

	N	%
Assess medication adherence regularly	9	82%
Assess readiness to change	5	29%
Evaluate lifestyle factors that could influence adherence	4	24%
Evaluate potential adherence barriers	3	18%
Assess patients' literacy level for educational materials	3	18%
Assess and address persistent symptoms	3	18%
Assess patients' regimen preferences	2	12%
Assess patients' goals for treatment	2	12%
Assess behavioral skills for medication adherence	1	6%
Review medication containers at each visit	1	6%

Interestingly, a majority of the guidelines (n=10, 59%) recommended multiple types of assessments (e.g., medication adherence, but also barriers to adherence, persistent symptoms, etc.), indicating the importance of health care providers' monitoring multiple influences and outcomes of medication adherence

5.7.5.5. Therapeutic Relationship, Communication, and Health Care Provider Factors

Thirteen guidelines (76%) made recommendations to improve the patient-provider relationship, improve communication between patients and providers, or otherwise improve health care providers' ability to address patients' medication needs and concerns.

The most common recommendations in this category were to involve the patient in treatment decisions (n=8, 47%) and to improve the therapeutic relationship (n=6, 35%). Guidelines were generally vague on specific steps providers could take to actually improve therapeutic relationship with patients. Particular recommendations that were offered included (in addition to including the patient in treatment decisions) improving communication, asking open-ended questions, being open-

minded about patient viewpoints and patients' right to autonomy, providing rationales for treatment recommendations, and asking patients about their specific concerns. Other less commonly recommended strategies included clinician training to address adherence; telephone resources and improved telephone support, particularly after initiation; involving other health care disciplines in a multidisciplinary intervention; expanding services for patients with poor adherence; and creating a medication adherence program or having written, updated adherence strategies.

5.7.5.6. Outside Influences and Co-Morbidities

The final category involved strategies to address outside influences on adherence and to manage co-morbidities. Six guidelines (35%) recommended engaging or improving family or other social support networks. Three (18%) suggested that health care providers should address financial barriers to adherence in some manner. Finally, one guideline recommended addressing substance abuse in patients with adherence concerns.

5.7.6. Discussion

The identified practice guidelines for improving adherence to medications demonstrated considerable variation in the recommendations provided. In many cases, the variation is likely due more to differences in the health condition or disease type on which the guidelines were focused, rather than on the scope of the guideline or the country of origin.

The quality of evidence in the guidelines varied considerably, with limited details about the methodologies used to determine the recommendations. Future guideline development work should incorporate reviews of existing research, as well as meta-analytic syntheses of tested interventions to determine the most effective intervention strategies for specific patient populations.

The guidelines often provided vague strategies, with few specifics. While the particular details for implementing adherence management strategies will certainly differ between clinical practice locations, guidelines can be more useful if they provide some specifics or examples to assist health care providers in developing the necessary skills and resources to better address adherence to medications. For example, Machtinger and Bangsberg[11] provide example scripts to use when interviewing patients about their medication regimen and to assess patient adherence. The general guideline by Aliotta, Vlasnik, and De Lor[24] provides a number of tools to assess factors such as social support, medication knowledge, and readiness to change.

Educational approaches have long been at the forefront of interventions necessary to improve adherence to medications. The guidelines, however, recognize that education to change health behaviors works best in conjunction with more active, behavioral approaches. It is clear that no approach to improve or manage medication adherence should rely solely on patient education.

Fewer than half of the guidelines recommended strategies addressing patients' motivation to change medication-taking behavior. Motivation is being increasingly recognized as a key factor in many types of health behavior changes. Motivation interventions are relatively new, compared to many of the intervention approaches for medication adherence. Additional research is needed at this point to further evaluate the effectiveness of approaches such as motivational interviewing and cognitive behavioral therapy as part of programs to improve medication adherence.

One piece that was noticeably missing from most guidelines was an algorithm to assist health care providers in determining what intervention strategies to use in which situations. While adherence management rarely fits a 'recipe' approach, for health care providers with minimal formal training in addressing adherence issues, practice algorithms can be a useful tool until the notice provider reaches a greater level of expertise in working with patients to improve and maintain effective medication adherence.

5.7.7. Conclusion and Recommendations

Given the high prevalence and high costs of medication non-adherence, it was surprising how few practice guidelines exist for improving and managing patient adherence to medications. Furthermore, the range of recommendations and differences in level of detail make comparing and evaluating the guidelines difficult. Future work in guideline development should be more clearly guided by research findings and appropriate synthesis of existing studies. Furthermore, comparative effectiveness research methods should then be used to evaluate guidelines to ensure that guideline implementation does yield improvements in adherence and health outcomes.

Few of the existing guidelines originated in European Union countries. Work should be conducted to adapt existing practice guidelines or develop new guidelines for adherence management that are congruent with the practical realities of the health systems and cultural norms of EU members. These guidelines should then be distributed to health care professional training programs for inclusion in the curricula for health care professional education.

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6 Identification and assessment of adherence-enhancing interventions

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6.1Summary

Background: Non-adherence to medications is prevalent across all medical conditions that include ambulatory pharmacotherapy, and is thus a major barrier to achieving the benefits of otherwise effective medicines.

Objective: The objective of this research was to identify strategies for enhancing adherence, and components thereof which successfully improve implementation of the prescribed drug dosing regimen and maintain long-term persistence.

Methods: MEDLINE, EMBASE, CINAHL, the Cochrane Library, and PsycINFO were systematically searched for randomized controlled trials that tested the efficacy of adherence-enhancing strategies with self-administered medications. The searches were limited to papers in the English language and were included from database inception to 28 April 2011. Our review included only studies in which adherence was reliably assessed by electronically compiled drug dosing histories.

Results: Sixty-five controlled clinical trials published between 1979 and April 2010 were included in the review. The linear regression model showed that the effect of interventions on adherence decreases 1% each month (p=0.0022). Intervention strategies that included feedback to the patients of his/her recent dosing history data were 8% more effective than intervention strategies that did not include such feedback (p=0.0142). The meta-analysis, conducted over 40 studies, showed that patients randomized to an intervention group had, on average, a combined adherence outcome which was 12% higher than in patients randomized to standard care. The average combined adherence outcome among patients receiving adherence-feedback was 21% [95%CI: 10%-32%] higher than among patients randomized to standard care. However, a large heterogeneity between studies, despite a common measurement, was evident across the studies. Only 4 studies reported a significant improvement in clinical outcome.

Conclusions: Notwithstanding the statistical heterogeneity among the studies identified, and potential publication bias, the evidence from our meta-analysis of RCT's employing unbiased methods of medication adherence measurements suggests that electronically-monitored adherence feedback is a potentially effective approach to enhance medication adherence. The limitations of this research highlight the urgent need to define guidelines and study characteristics for research protocols that can guide researchers in studies designed to assess the effects of adherence-enhancing interventions.

6.2 Introduction

Adequate adherence to medications of proven efficacy and acceptable safety is essential for realizing their health benefits. Yet, suboptimal adherence to prescribed medication regimens is prevalent across all clinical conditions and populations[1].

In the setting of chronic conditions, non-adherence to medications generally worsens outcomes of treatments, leading to increased risk of adverse medical events, more consultations with physicians, higher rates of hospitalization and increased health care costs[1-5]. Non-adherence has recently been estimated to cost the US health care system $310 billion annually[6] with the associated economic burden being specific to disease severity, co-morbidity and the respective severities of co-morbidities[7].

Many reasons exist for non-adherence to medicines and knowledge of these could help clinicians to target persons in need of intervention, design these interventions, and help researchers to plan studies of adherence.

Several reviews[8-10] of interventions for enhancing adherence to medications have consistently highlighted methodological weaknesses in the study designs and methods used, often precluding quantification and permitting only qualitative assessments. In particular, there are major between-study differences in methods used to assess adherence, differing not only in reliability but also in the degree of temporal resolution of their measurements. These methodological differences have thus hampered the identification of interventions that can effectively enhance adherence to medications.

Among the different measurement methods available, electronic medication-event monitoring, which consists of automatic compilation of the time-history of each patient's entry into the drug package, has been considered to provide the most reliable data on adherence in complex clinical situations and in the setting of clinical trials and adherence research[1]. Moreover, it has been reported that electronic medication-event monitoring is the most accurate method for identifying non-adherence[11-13]. Several studies confirm that package opening times are a robust indicator of the times at which patients take the prescribed doses[14-16].

Electronically-compiled dosing histories may also be used as part of the adherence-enhancing intervention, by allowing the health professional to provide feedback to the patient on his/her dosing history. This approach has been referred to as "Measurement-Guided Medication Management (MGMM)"[4].

6.3 Objectives

The objective of this research was to systematically search the literature to identify randomized controlled trials containing empirical data on the efficacy of interventions to enhance adherence to prescribed medications, as assessed by electronic medication-event monitoring methods.

6.4 Methods

The report of this systematic review follows the PRISMA guidelines[17].

6.4.1 Eligibility criteria

We included randomized controlled trials (RCTs), including cross-over and cluster-randomized trials, containing empirical data on interventions expected to enhance adherence to prescribed medications in adults and pediatrics assessed by electronic medication-event monitoring methods.

6.4.2 Exclusion criteria

Papers were excluded for the following reasons:
(a) Studies that did not focus on adherence to medications; (b) Studies where adherence was not measured electronically in all patients enrolled in the clinical trial; (c) Studies that were not RCTs; (d) Studies that focused on interventions to improve disease or symptom management; (e) Studies that focused primarily on measurement and did not include an intervention; (f) Studies where no quantifiable adherence data were reported; (g) Studies that did not report a formal comparison of adherence data between intervention and control conditions; (h) Double citations. No paper was excluded on the grounds of quality.

6.4.3 Information sources

MEDLINE, EMBASE, CINAHL, the Cochrane Library, and PsycINFO were searched for all papers testing adherence-enhancing interventions. The searches were limited to papers in the English language and were included from database inception to 28 April 2010. Detailed search strategies specific to the different databases are provided in Appendix 6.1.

6.4.4 Study selection

Eligibility assessment of title and abstract was performed independently in an unblended standardized manner by two reviewers (JD, TR). If one reviewer coded a study as potentially eligible, the paper was included for full-text review. The full texts of potentially eligible papers were retrieved and reviewed in the second stage of the screening process. Disagreements were resolved by discussion and a final decision was reached between the two reviewers.

6.4.5 Data collection process

A structured data collection sheet was developed to extract data from each study. All data were extracted from the papers; no additional information was sought from authors. The following paragraphs describe which data were extracted.

6.4.6 Data items

Adherence definitions

A range of variables were extracted, according to reporting in the primary studies. These were labeled as follows over the relevant reporting period:

- *Correct dosing* was defined as the percentage of treatment days with the correct number of doses taken;
- *Taking adherence* was defined as the percentage of prescribed doses taken;
- *Timing adherence* was defined as the percentage of doses taken within a pre-defined time window;
- *Percentage of adherent patients* was defined as the percentage of patients with adherence measures greater than a pre-defined value.

Data on mean adherence outcomes were extracted for each reported adherence variable, with a 95% confidence interval (CI) or standard deviation (SD) for all the study groups.

Data on clinical outcomes were extracted and reported as a significant or non-significant difference between the study groups. We did not assess the quality of the selected studies in regards to whether or not the study was appropriately powered to detect differences in adherence or in clinical outcomes.

Studies with small sample sizes were included. Although they often lack statistical power, small studies sometimes contribute novel interventions or target difficult-to-recruit populations.

Categorization of interventions

The adherence-enhancing components were classified in 8 categories, based on a taxonomy developed from other sources[10;18-20].

- Interventions based on a *treatment simplification* (TRT simpl): consisted of changes in the dosage schedule (e.g. once daily vs twice daily) or a change in formulation (e.g. change from tablets to liquid formulation);

- *Cognitive – Educational interventions* (Cogn-Educ) present information individually or in a group setting, delivering it verbally, in written form, and/or audio-visually. These interventions are designed to educate and motivate patients based on the concept that patients who understand their condition and its treatment will be more informed, more empowered, and more likely to adhere[10;18;19];

• *Behavioral – Counseling interventions* (Behav-Counsel) shape and/or reinforce behavior, empower patients to participate in their own care, while positively changing their skill levels or normal routines (e.g. skill building by a health care professional, pillboxes, calendars, steps intended to remind the patient to take the medication or tailor the regimen to the patient's daily routine)[10;18;19]

• *Social – Psycho-affective interventions* (Soc-Psych) focus on patients' feelings and emotions or social relationships and social support (e.g. family counseling, group meetings with peers or another groups, stress management, problem solving)[10;19]; as long as the interventions are based on the assumptions that cognitions can be monitored and altered, and in turn may facilitate behavior change[20];

• Interventions based on *electronically-monitored adherence feedback* (*EM-feedback*): were designed to provide feedback on patients' dosing histories compiled from electronic medication-event methods;

• Interventions based on *technical reminder systems* (*Tech rem*): were designed to provide technical devices to remind the patients when it is time to take their medications (e.g. mobile phone text message, pager, electronic monitor with beeper);

• Interventions using technical equipment for monitoring the disease being managed (*Tech equip*): were designed to use various technologies to provide patients with feedback on a clinical outcome (e.g. glucose meter, BP home measurement, feedback on laboratory results);

• *Rewards*: any kind of rewards for adhering to medication (e.g. cash reinforcement, toys for children).

6.4.7 Summary measures

The outcome variable in the analysis is the reported effect of interventions on all reported adherence measures. If outcomes were reported at several time points, the most distal time points from the end of the intervention were coded.

When more than one type of intervention arm was tested in a study, each arm was considered as a separate data point.

6.4.8 Synthesis of results

Descriptive statistics (mean, median, SD, minimum, maximum) were used to summarize the structured data retrieved from the reviewed papers. Box-whisker plots were used to illustrate the data graphically.

To study the association between the adherence-enhancing components and their effect on adherence, a combined adherence outcome was defined by selecting the available adherence summary variable in the following order: correct dosing, taking adherence, timing adherence, and percentage of adherent patients. As each study may report the result of the adherence intervention using one summary variable and not the others, the definition of this combined adherence outcome was intended to take into account all studies available for the analysis. Unless otherwise specified, the analysis is based on this combined adherence outcome measure. The interchangeability of these adherence measures was verified by including significant variables that indicate the use of each of these measures in the model.

The mean adherence (point estimate) was considered for this analysis. The dependent variable of the model is the difference of the adherence outcome between the intervention and control groups of each study. In the model building process, the effect of each available potentially confounding factor on the combined adherence outcome was tested using a linear meta-regression model.

The following were included as explanatory variables: medical condition, unit of allocation at randomization (randomization by patients or centers), average age, percentage of females, number of subjects in the intervention group, study duration (in weeks), the type of adherence outcome measure used in the analysis, the category of adherence-enhancing intervention, and the effect of the occupation of the person delivering the intervention (physician, nurse, pharmacists, or support partner). A stepwise regression procedure with forward selection and t-statistic equal to 2 was used to define the final model.

For the studies in which the SD of the adherence outcome was reported together with its mean, we conducted a more formal estimation of the adherence-enhancing effect, measured by the difference of the adherence outcome of each intervention and the control group of each study (and aggregated 95% confidence interval) resulting from the different intervention types identified.

For this meta-analysis, random-effects models were used to estimate the true effects by considering the differences in the methods and sample characteristics of the included studies. In this model, the average effect was estimated using weighted least squares where the weights correspond to the inverse of the combined true heterogeneity between studies and the variation due to sampling error within each study.

Total variability due to heterogeneity (I^2) and Q-test from the random effects model were used to assess the statistical heterogeneity of the studies.

6.4.9 Risk of bias across studies

A funnel plot was used to assess the presence of publication bias across studies.

6.5 Results

6.5.1 Study selection

Sixty-five randomized controlled trials were included in the review. An overview of the review process and reasons for exclusion at the different steps are displayed in Figure 6.1.

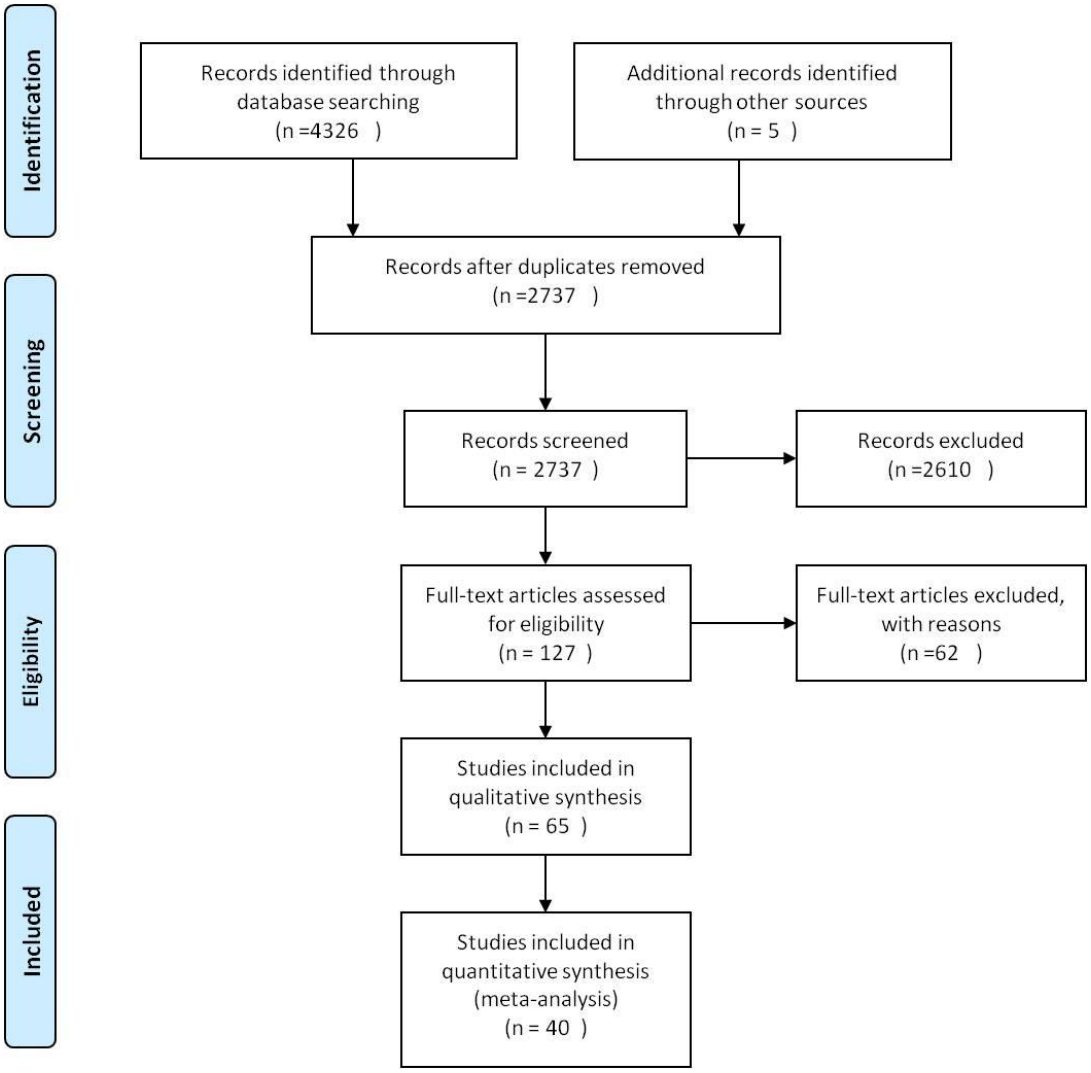

Figure 6.1
Flow diagram of study selection process

6.5.2 Study characteristics

Individual study characteristics are listed in Appendix 2. The majority of the studies were 2-arm studies with one intervention group compared with one control group. However, 4[21-24] of the 65 studies were 3-arm or 4-arm studies testing the efficacy of more than one adherence-enhancing component, each compared with the same control group. We therefore extracted outcome data and performed the analysis on 70 intervention groups.

Within our selected randomized controlled trials, five were cluster randomized[25-29], and two were cross-over studies[30;31]. The publication years ranged from 1979 to 2010 with a peak in 2007 (n=12). Out of 5 cluster-randomized studies, 3[25;26;28] took into account the within cluster (within center) correlation to analyze the adherence intervention effects. The principal studies characteristics are summarized in Tables 1, 2 and 3.

Table 6.1. Treatment characteristics of the 70 intervention groups

Medication intake	
• Oral	
• Inhalation	
• Eye drops	
Dosing regimens	
• Once daily	
• Twice daily	
• Once daily vs twice daily	
• Once daily vs once weekly	
• Variable (e.g. the medication with most frequent pill-taking schedule	
• Not reported	
Occupation of the person delivering the intervention	
• Nurse	
• Physician	
• Others (research assistant, comm health worker, social worker,…)	
• Pharmacist	
• Support Partner	
• Psychologist	
• Not reported	
Place where the intervention was provided	
• Hospital	
• Home	
• Hospital & Home	
• Pharmacy	
• Primary care office	
• Community health care center & Home	
• Private practice & Home	
Electronic medication-event monitoring	
• MEMS™	
• Smartinhaler	
• MDI chronolog	
• Doser CT	
• RemindRX	
• Dosing Aid	

Table 6.2. Group of patients targeted by the interventions in the 70 intervention groups

Subject targeted by the intervention	
• Adult Patient	
• Children & Parents	
• Adult Patient & Healthcare Provid	
• Healthcare Provider	
• Couples	
Specific population targeted by the intervention	
• Children	
• Socio-economically disadvantage patients	
• Women	
• Postmenopausal women	
• Depressed patients	
• Soldiers	
• Patients with memory impairment	
• Adults commonly underrepresente research (female, African America Hispanics)	
• Pregnant women	
• Elderly	
• Methadone clinic patients	
• None	

Table 6.3. Demographic characteristics of the 70 intervention groups by randomization group

	Usual care	**Intervention Group**
Mean sample size expressed as number subjects (min-max) (n=64)	68.72 (6[58]- 1113[25])	71.14 (4[66] – 1189[25])
Average age expresse in years (min-max) (n=	48.42 (3.80[62]-73.70[22])	47.88 (3.40[62]-76.20[22])
Gender expressed as female (n=51)	50.54%	49.95%
Ethnicity expressed as %Caucasian (n=26)	41.83%	45.20%

Disease categories were broad (20 different diseases); studies exclusively reported patients with chronic diseases. The majority of studies (n=25) were from the field of HIV infection.

The number of medications monitored by electronically compiled drug dosing histories ranged from 1 to 4 in each patient. In most of the studies (n=57), medication adherence was assessed electronically for 1 medication. In studies with multiple medications for 1 indication, the medication with the most frequent or the most complicated dosing regimen was monitored. In the majority of these studies, however, adherence-enhancing interventions aimed at enhancing medication adherence with all prescribed medications. In 4 studies[32-35] it was not clear which and how many medications were monitored.

6.5.3 Intervention characteristics

In 33 intervention groups, the efficacy of only one adherence-enhancing component was tested against a control group, whereas in 37 intervention groups a combination of multiple adherence-

enhancing components was tested. Figure 6.2 depicts the combinations of adherence-enhancing component across the different studies. Average patients' follow-up duration ranged from 4 weeks[36] to 15 months[37.]

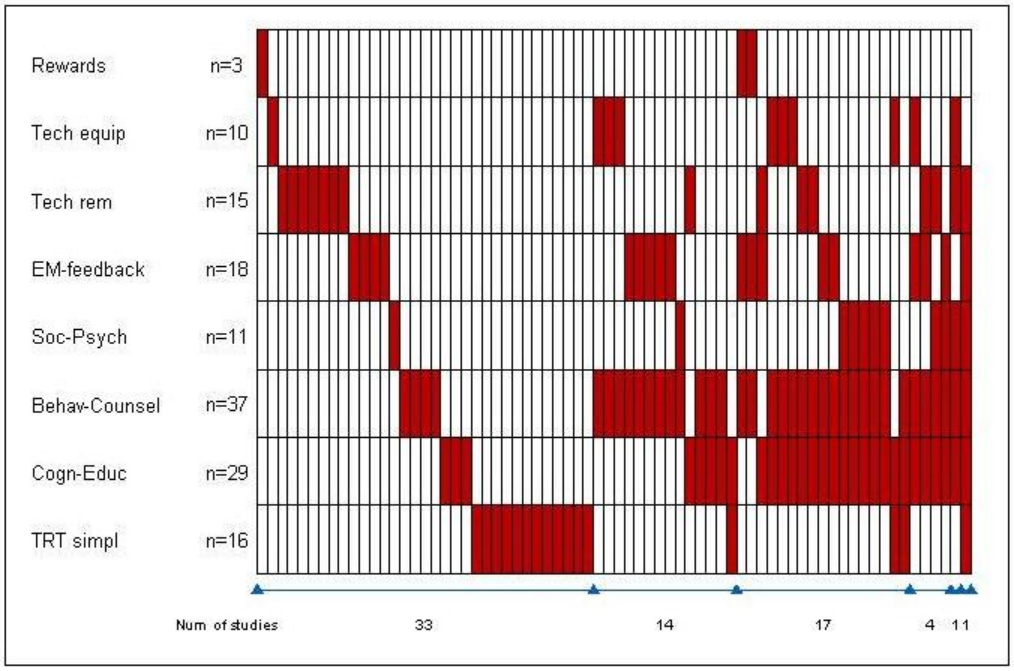

Figure 6.2

Combination of adherence-enhancing components for each intervention group (n=70) (each column= 1 intervention group; Studies are ranked by number of intervention types tested); Rewards: any kind of rewards for adhering to medication; Tech equip: Interventions based on a technical equipment use; Tech rem: Interventions based on a technical reminder use; EM-feedback: Interventions based on EM-adherence feedback; Soc-Psych: Social – Psycho-affective interventions; Behav-Counsel: Behavioral – Counseling interventions; Cogn-Educ: Cognitive – Educational interventions; TRT simpl: Intervention based on treatment simplification.

In 2 studies[33;36], the intervention was delivered only on one occasion to the patients. In these 2 studies, the patient post-intervention follow-up period ranged from 1 month[36] – 3 months[33]. The adherence-enhancing interventions showed significant effects on adherence outcomes in these studies.

The frequency with which the intervention was delivered to the patients was not included as variable in the meta-analysis. In studies in which multiple intervention components were part of the adherence-enhancing intervention, each intervention component was reported with a different frequency. In several studies the frequencies were not clearly described[34;38;39].

Only 3 studies[40-42] provided an estimate of the intervention's costs. The first study[40] reported that the price for an alarmed vial used for 4 weeks ranged from 16 US dollars to 80 US dollars (2001). The second study reported a cost of 205 US dollars per patient[41] for a 1-year intervention delivered by a trained pharmacist providing patient centered instructions and education (2007). A third study[42]

reported an intervention based on daily text message reminders sent to the patients over a 4 week period (costs estimated per patient: 3.60 US dollars, projected costs per year: 46.80 US dollars; 2009). No further conclusion on intervention costs could be derived given the limited information and the diversity of the studies.

6.5.4 Health outcomes

Among the studies that reported data on clinical outcomes (n=32), only 4 studies[32;43-45] reported a significant difference in clinical outcome between the intervention and the control groups.

Bogner et al.[32] reported fewer depressive symptoms (CES-D mean scores difference between groups: 9.3; p<0.01), lower systolic blood pressure (systolic BP difference between groups: 14 mmHg; p<0.01), and lower diastolic blood pressure (diastolic BP difference between groups: 9.2 mmHg; p<0.01) in hypertensive patients randomized to the integrated care intervention compared to participants in the usual care group at 6 weeks of treatment.

Kardas[43] noted a greater decrease in the mean weekly number of chest pain episodes in angina pectoris patients randomized to the once daily dosing group compared with the patients randomized in the twice daily dosing group (0.94 +/- 4.32 and 0.30 +/- 1.20 episodes per week for the once and twice daily regimens, respectively; p<0.0001).

Kardas et al.[44] reported that patients in the once-daily group achieved significantly better glycaemic control than those treated with the twice daily medication (HbA1c level difference between groups: 0.9%; p<0.0001).

Rudd et al.[45] found that hypertensive patients randomized to the intervention group achieved greater reductions in office blood pressure values at 6 months than those receiving usual care (systolic BP difference between groups: 8.5mmHg; p<0.01; diastolic BP difference between groups: 1.4mmHg; p<0.05).

6.5.5 Synthesis of the results

Adherence data collected from the 70 intervention studies resulted in drug dosing history data compiled among 8995 ambulatory patients. The median difference in adherence measures between the control and intervention group at the end of the study in studies that reported adherence as “taking adherence” (n=44) was 8.7% (range: -10.4, 37.0%; IQR: 13.58), in studies that reported “correct dosing” (n=21), the median difference was 14.5% (range: 1.4, 30.0%; IQR: 13.90) in studies that reported “timing adherence” (n=10), the median difference was 18.9% (range: 2.0, 27.0%; IQR: 9.95) and in studies that reported the “percentage of adherent patients” (n=13), the median difference was 20.0% (range: 1.8, 59.0%; IQR: 17.44). The median difference in the combined adherence outcome was 12.8% (range: -10.4, 59.0%; IQR: 17.60) (Figure 6.3).

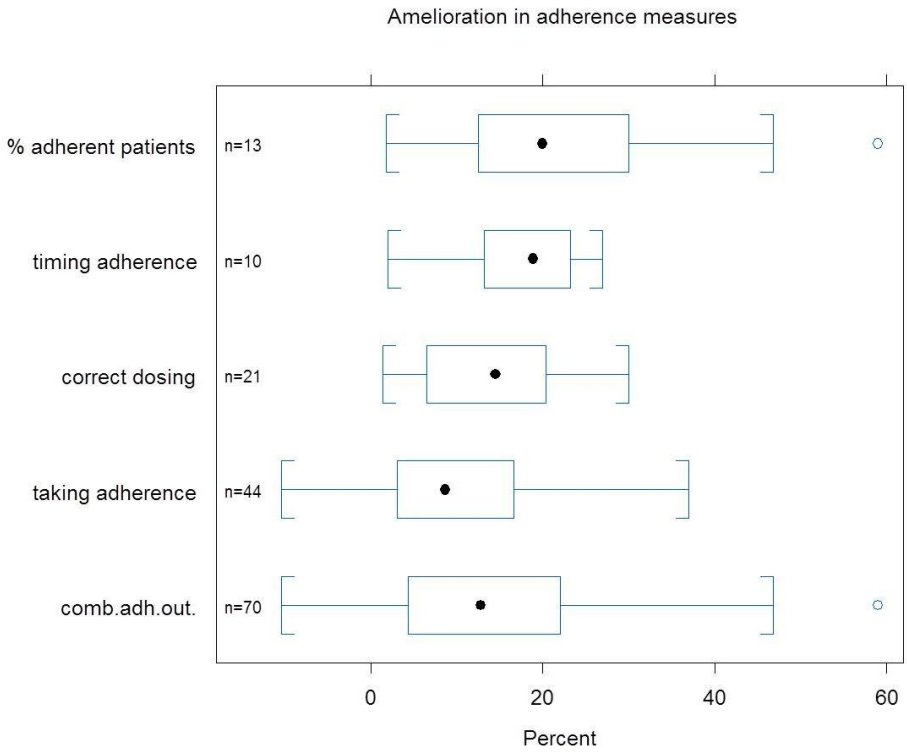

Figure 6.3

Differences in adherence outcomes (%) by type of adherence measures.

% adherent patients: the percentage of patients with adherence measures greater than a predefined value (IQR: 17.44); timing adherence: the percentage of doses taken within a pre-defined time window (IQR: 9.95) ; correct dosing: the percentage of days with the correct number of doses taken (IQR: 13.90); taking adherence: the percentage of prescribed doses taken (IQR: 13.58); comb.adh.out.: combined adherence outcome (IQR: 17.60)

Potential confounding factors and intervention components that affect adherence measures

Univariate linear regression models were used to explore the association between each potential confounding factor and the difference in adherence measures between the control and intervention group. The models showed that study duration was the only factor that significantly affected adherence measures (p=0.0022). The model showed that the longer the patient follow-up, the smaller the difference in the adherence outcome between the study groups at the end of the study (Figure 6.4). For each month longer, the effect diminished by 1%.

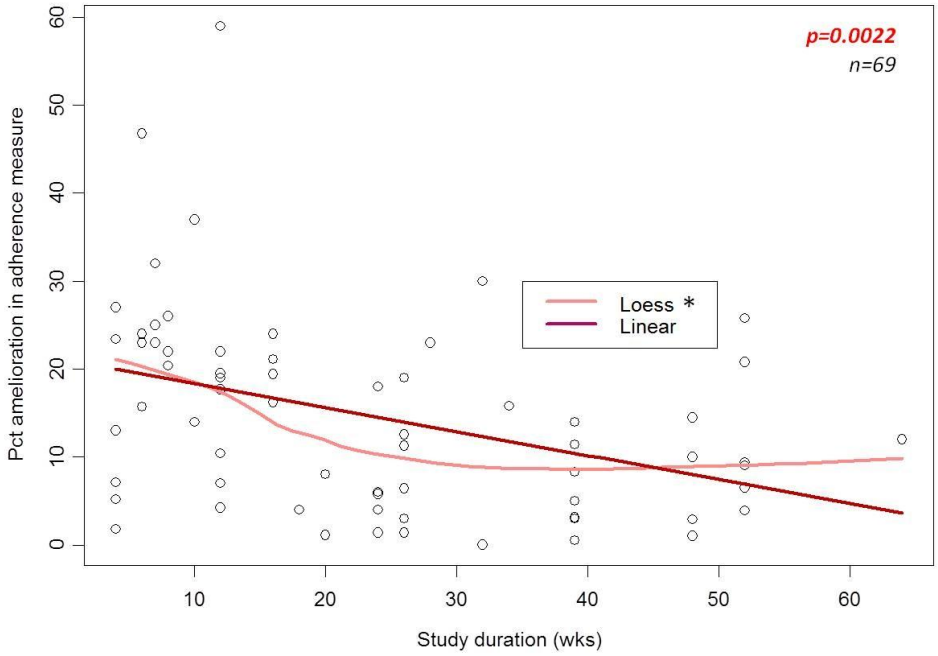

Figure 6.4

Amelioration of adherence measures by study duration (linear regression model). *Loess: locally weighted scatterplot smoothing

The number of subjects enrolled in the intervention group, subject gender and average patients' age in the intervention group did not significantly affect this difference. There is no significant effect of an increase in the number of intervention elements on the adherence outcome (p=0.1227). The results of the univariate linear regression model are summarized in Table IV. The unit allocation of randomization, either by patients or by centers, had no significant effect on the difference in the adherence outcome between the study groups at the end of the study (Rank-sum test; p=0.9002).

Figure 6.5 depicts the differences in the adherence outcome by intervention component tested in the intervention. Studies that included an EM-feedback type were 8% more effective than studies testing intervention strategies that did not include such feedback (Rank-sum test; p=0.0142).

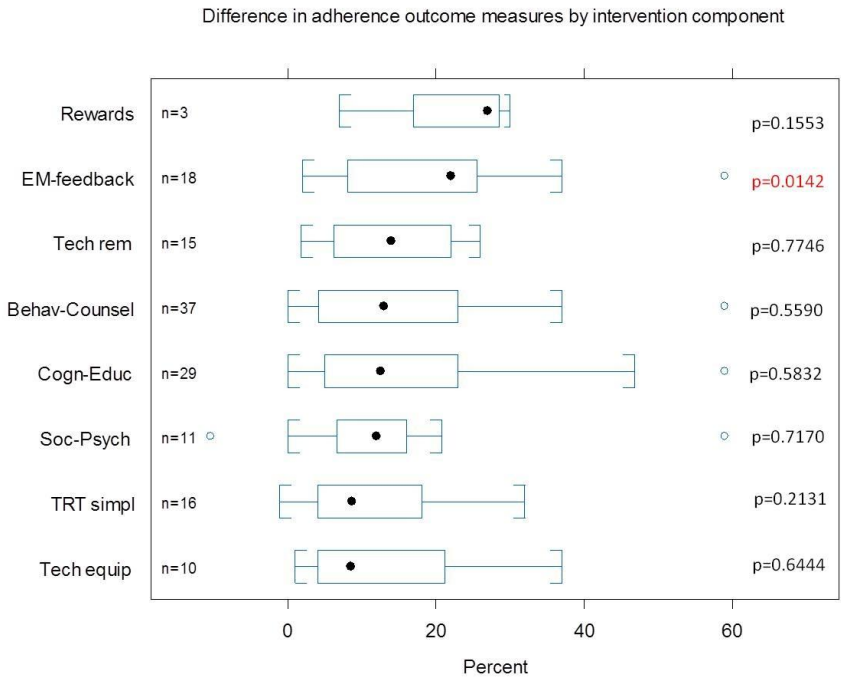

Figure 6.5: Difference in the combined adherence outcome (expressed as percentages) by adherence-enhancing component.

Rewards: any kind of rewards for adhering to medication; EM-feedback: Interventions based on electronic-monitoring adherence feedback; Tech rem: Interventions based on a technical reminder use; Behav-Counsel: Behavioral – Counseling interventions; Cogn-Educ: Cognitive – Educational interventions; Soc-Psych: Social – Psycho-affective interventions; TRT simpl: Intervention based on treatment simplification; Tech equip: Interventions based on a technical equipment use

The occupation of the person who provided the intervention had no significant effect on adherence measures (Rank-sum test; Physician p=0.7961; Nurse p=0.5454; Psychologist p= 0.8862; Pharmacist p=0.8397; Support Partner p=0.8080).

Significant factors that affect adherence outcomes: results from the multiple regression model

When all variables were analyzed in a multiple regression model using a stepwise method, the variable indicator of EM-adherence feedback type was the only intervention component that remained significant in the final model (p=0.0012). The model estimates a 9.4% increase of adherence measure when the intervention includes an electronically monitored adherence feedback system.

Study duration is also a significant factor that affected adherence measures (p=0.0008). The variable "percent adherent patient" indicator (equal to 1 when the percentage of adherent patients is used as outcome variable, 0 otherwise) is significant in the model (p=0.0225), indicating that the percentage of adherent patients is not interchangeable with other adherence measures (correct dosing, taking

adherence, timing adherence). The inclusion of the indicator variable in the model then serves a correction when this percentage of adherent patients is used as an adherence measure.

Effects of adherence-enhancing interventions on adherence outcomes: results from the meta-analysis

Forty studies, among the remaining 65 studies, reported a SD and also reported adherence as the following variables: “correct dosing” (n=12); “taking adherence” (n=24); “timing adherence” (n=14).

The forest plot reported in Figure 6.6 illustrates the percentage point differences in the adherence outcome between intervention and control groups from the individual studies as well as the estimated overall percentage point difference on adherence. The overall percentage point difference between intervention and control groups of the 40 studies was 12.21% [95%CI: 8.58-15.84]. One can see a wide variability in percentage point differences and confidence intervals between studies.

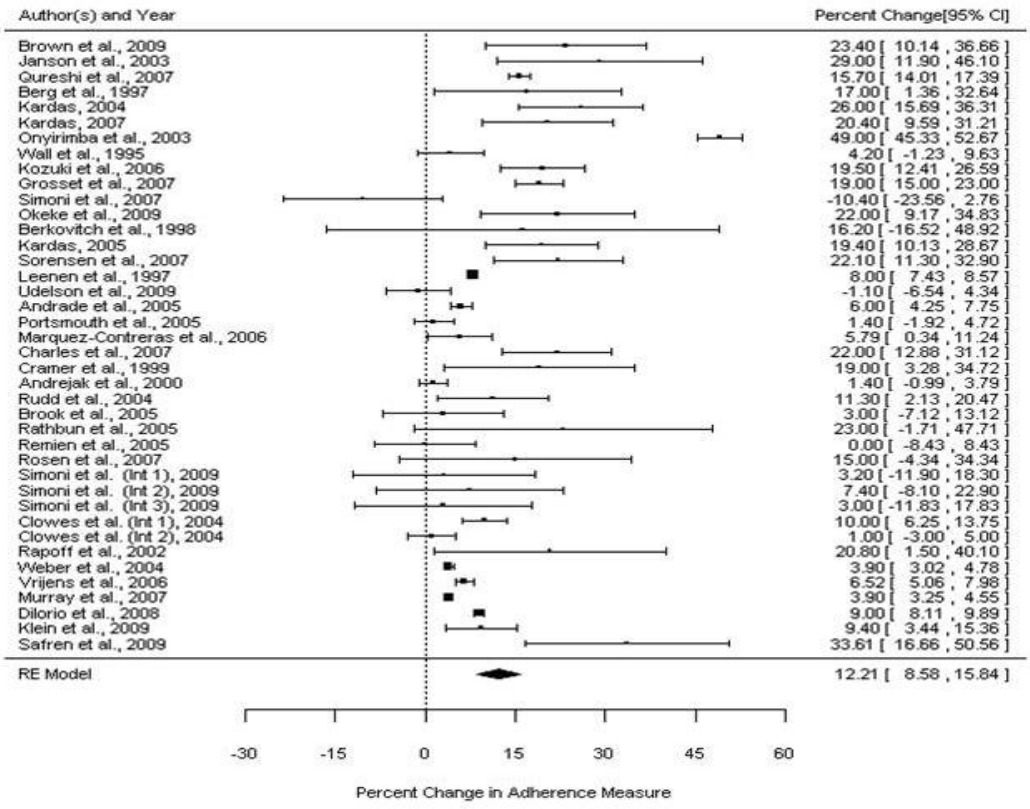

Figure 6.6

Percentage point differences in adherence outcomes (ordered by duration of follow-up: 4 weeks- 52 weeks; n=40)

Figure 6.7 illustrates the percentage point differences in the combined adherence outcome in studies that tested the EM-adherence feedback type as part of the intervention. The overall percentage point

difference of these studies was 20.90% [95%CI: 9.85-31.96]. The overall percentage point difference was 9.67% [95%CI: 6.65-12.69] for the studies that did not test the EM-adherence feedback type as part of the intervention (Figure 6.8).

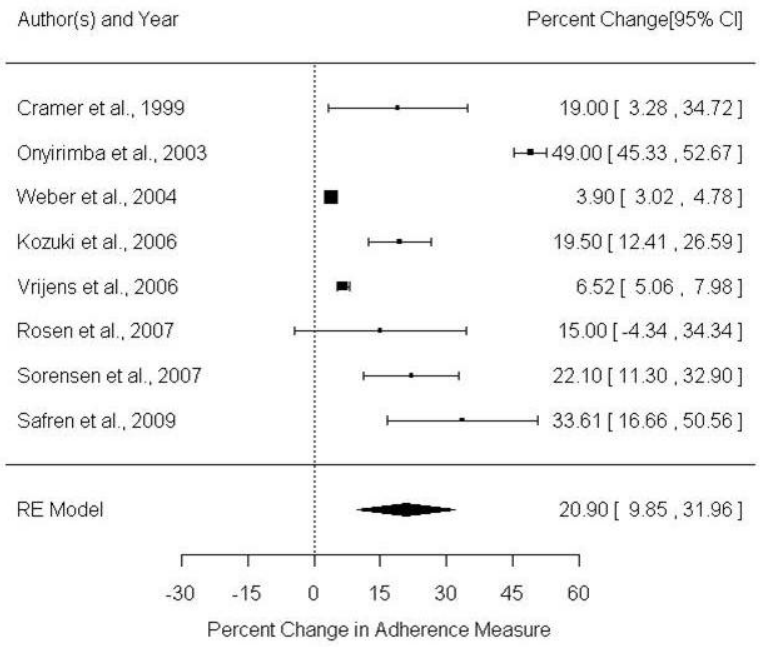

Figure 6.7

Percentage point differences in the combined adherence outcome in studies testing an EM-adherence feedback type (n=8)

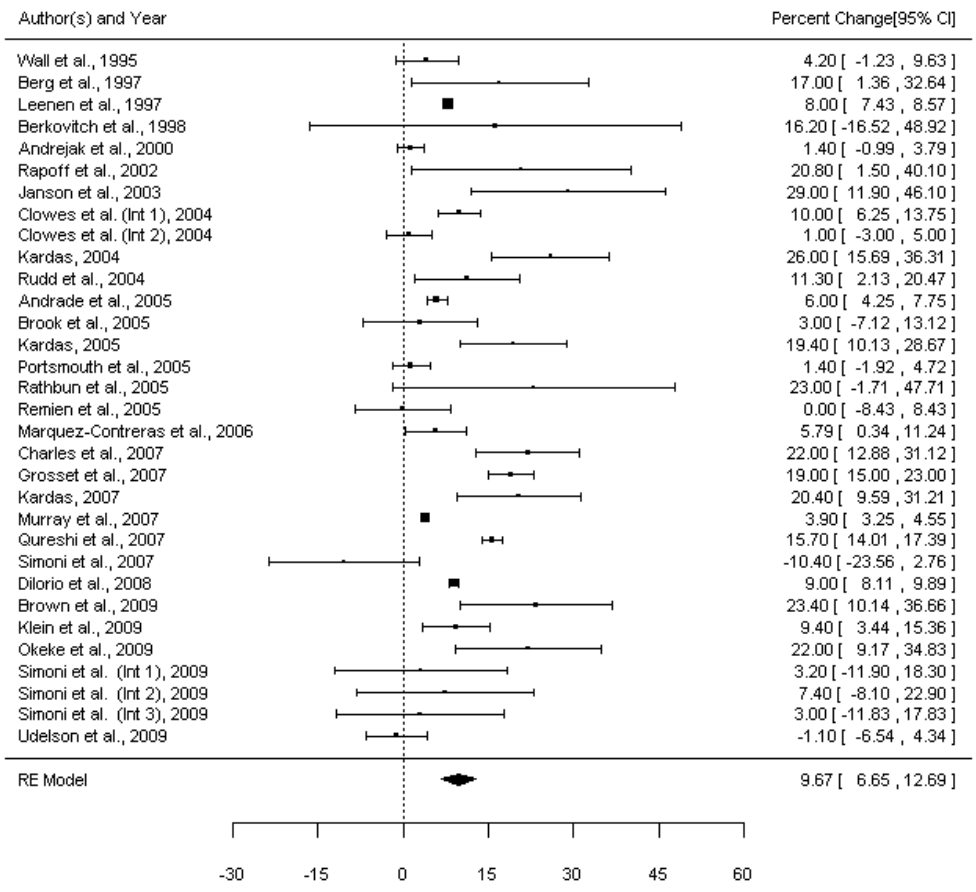

Figure 6.8

Percentage point differences in the combined adherence outcomes in studies not testing an EM-adherence feedback type (n=32)

6.5.6 Risk of bias across studies

The Random-Effects Model, used to test the heterogeneity, was significant ($p<0.0001$) and showed that the studies were not homogenous ($Q(df = 39) = 961.3253$, $p<0.0001$).

Percentage of total variability due to heterogeneity (I^2) based on this model is estimated as 98.88%, again showing that the studies were heterogeneous. The funnel plot (Figure 6.9) shows possible publication bias in studies with high variability of the intervention effect. Studies with large intervention effects gave low p-values despite of their high standard errors and studies with $p<0.05$ were more likely to be published.

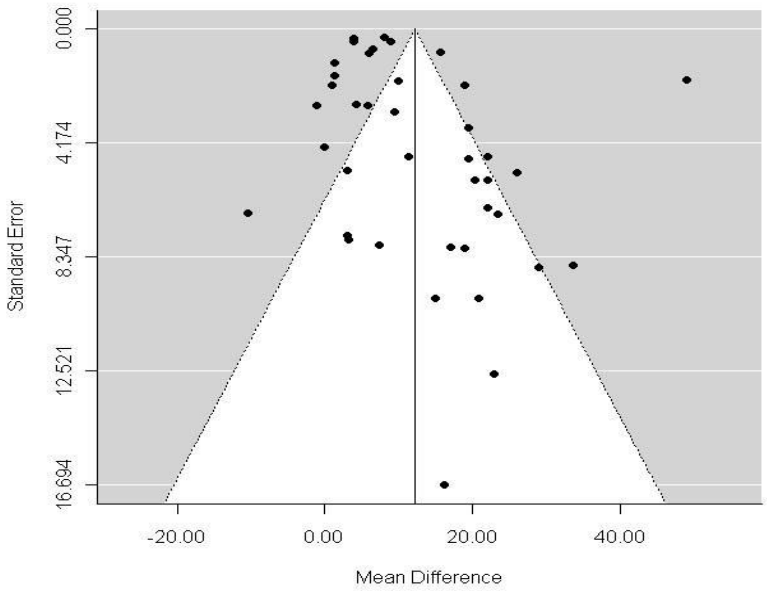

Figure 6.9

Funnel plot to assess any publication bias across studies

6.6 Discussion

In this systematic literature review, we identified 70 pair-wise comparisons of interventions published in 65 RCTs intended to enhance patient adherence to prescribed medications. All included studies assessed adherence to medication through electronic compilation of drug dosing history data.

Patients randomized to an intervention group, had, on average, an adherence outcome which was 12% higher [95%CI: 9-16%] than in patients randomized to standard care. This effect size is similar to the value reported in Peterson et al.[46]. These authors conducted a meta-analysis on adherence-enhancing intervention trials and reported an overall effect size of 4 to 11%, but no single strategy appeared to be best. The meta-analysis conducted by Roter and colleagues[47] reported also that no single approach is better than another at improving medication adherence.

In this review, intervention strategies which included a focused discussion based on giving feedback to the patient of his/her recent dosing history data, compiled by electronic monitors (EM-feedback), were significantly more effective than intervention strategies that did not include such feedback (p=0.0142). This finding is consistent with the results of Kripalani and colleagues[19] who reported that the most common and effective forms of intervention were dosage simplification and repeated assessment of medication adherence with feedback. They included studies which reported at least 1 measure of medication adherence and 1 clinical outcome, with at least 80% follow-up of patients during 6 months in chronic medical conditions only. The methods of adherence measure varied widely in their studies.

Another study recently highlighted that EM feedback can be a clinically useful tool when used in combination with other adherence-promoting treatment strategies aimed at enhancing medication adherence among chronically ill youth[48].

Measurement Guided Medication Management (MGMM) of adherence may thus be an approach to enhance adherence to medications in which reliable, detailed, recent, electronically-compiled drug dosing history data are provided as feedback to the patient on his/her adherence to prescribed medications. It sets the stage for focused dialogue between the healthcare providers and their patients reinforcing behavioural, social and cognitive interventions.

There was an average difference of 21% [95%CI: 10%-32%] in the combined adherence outcome between patients receiving EM-feedback versus control group—more than double the average difference among patients receiving an intervention that did not include the EM-feedback versus control group: 10% [95%CI: 7% - 13%]. Other intervention components did not show any significant effect on the combined adherence outcome. Conn et al.[49] reported a larger adherence effect size for interventions employing special medication packaging, dose modification, participant monitoring of medication effects and side effects, succinct written instructions, and standardized (not individualized) interventions. But, the difference with our review is that they included studies in which adherence was mainly assessed by pill-count, the unreliability of which is well-documented[50].

The duration of the study follow-up showed a significant effect on the improvement in the combined adherence outcome, suggesting that the intervention effects on adherence tended to diminish over time. This evident diminution in improvement has an important clinical implication that it may not be realistic to expect a single episode of adherence-enhancing intervention to have long-lasting effects. In 2 studies[33;36], the intervention was delivered on one occasion. The effects of the adherence-enhancing interventions on adherence outcomes were statistically significant but the short follow-up period following the once-delivered intervention does not allow for an estimation of the intervention's waning effect over time. Interventions may have to be provided in a sustained fashion as an integral part of the treatment plan in order to achieve and maintain adherence.

In a recent review, Haynes *et al*.[9], reported that several simple interventions appeared to improve adherence with short-term regimens, but interventions to improve medication use for chronic conditions appeared less effective overall and were often multifaceted, making it more difficult to synthesize published evaluations. The latter concurs with our opinion, and was also highlighted by McDonald *et al*[10], that most studies included in our review assessed successfully complex interventions but did not assess the separate effects of the components, begging the question of whether all elements were required.

It highlights, nevertheless, that several interventions were effective in improving adherence to medications. Few of them were however able to demonstrate an impact on clinical outcomes. While data on clinical outcomes were reported in 32 studies, only 4 studies[32;43-45] reported a significant

difference in the effect of adherence-enhancing interventions on clinical outcomes. Of note is that most studies were not powered to show a difference on clinical outcomes, nor did they control for other potential influences on the clinical outcomes. Kripalani and colleagues[19] reported almost the same conclusion. Only a few of the included studies in their review demonstrated an impact on clinical outcomes, although they included only studies in which at least 1 measure of clinical outcome was reported.

6.6.1 Main findings and conclusions

To our knowledge, this is the first review to focus only on studies in which dosing histories were electronically compiled, at rates of data sampling high-enough to provide adequate definition of when doses were or were not taken. Despite several limitations, this review supports the effectiveness of EM-adherence feedback to patients of their recent dosing history data.

6.6.2 Strengths and limitations

A major strength of this research is that it includes only studies that used electronically-compiled drug dosing histories, which is considered to be the most reliable and the most detailed approach for estimating adherence to medications. Consequently, however, only a small proportion of adherence-enhancing interventions are included in this review.

This meta-analysis was limited by the heterogeneity of the pooled data and the different measures of medication adherence.

Furthermore, we included each randomized controlled trial testing adherence-enhancing interventions. We did not apply any quality appraisal during the paper's selection process.
Given that the review is limited to EM monitoring of adherence, we have probably included more studies of MGMM than a review with broader inclusion criteria for adherence measurement. A publication bias might exist because only significant MGMM studies might be published, and inferior comparators might be used (investigators are sold to the concept of MGMM, and are "EM practitioners"). One might consider that the outcome measure and the intervention are almost one and the same thing.

Among the RCTs reviewed, considerable variability was evident with respect to: study size, randomization method, frequency of intervention repetition, potential bias, operational definition of adherence, identification of the intervention types, study follow-up, definition of standard of care, inclusion criteria used. To the contrary of our review, McDonald et al.[10] conducted a descriptive review of the included studies instead of a quantitative summarization (ie, meta-analysis) of findings across studies because of the heterogeneity in the methodology of adherence-enhancing intervention studies.

Few papers described clearly the methods used. This problem, also highlighted by several other authors[9;51-54], led to discrepancies in data extraction between the two reviewers that needed to be resolved. A majority of studies reported significant differences in at least one adherence measure between the study groups (59 significant differences vs 27 non-significant differences), but a potential publication bias across the studies was identified through the funnel plot. We did not search conference abstracts and other sources to quantify this potential bias.

6.6.3 Implications and recommendations

The limitations of this research highlight the need to define guidelines and study characteristics for research protocols that can guide researchers in the design, conduct, and analysis of studies designed to assess the effects of adherence-enhancing interventions[53;54]

Because there is a broad spectrum of reasons for non-adherence, including unintentional as well as intentional, any single intervention is not likely to address all determinants. Future clinical trials should:

- be better executed (statistically robust, adequately powered for a clinical endpoint, using a sound adherence measure etc);
- test a range of adherence-enhancing interventions to acknowledge the multifaceted nature of non-adherence;
- aim to identify those patients most likely to respond to one form of intervention versus another;
- acknowledge that adequate patient follow-up is necessary to ascertain long-term efficacy of interventions;
- estimate the impact of adherence-enhancing interventions on clinical outcomes[9;49];
- acknowledge that the efficacy of adherence-enhancing interventions wane over time, requiring repeated administration;
- test the dose and frequency with which the intervention is offered to the patients;
- place greater emphasis on testing adherence-enhancing interventions in real life settings.

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7 Report on the cost effectiveness of interventions that promote adherence: a systematic review of the literature and economic evaluation

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7.1 Summary

Decisions concerning the reimbursement of health technologies are informed increasingly, across several jurisdictions, by evidence of their cost-effectiveness. This applies equally to interventions aimed at improving adherence to medications – those that are not deemed to be cost-effective do not represent good value for money, and are less likely to be reimbursed by payers of healthcare and/or delivered by healthcare providers.

The aim of work package six was to generate economic evidence to inform policy and practice about adherence-enhancing interventions. The work package included a systematic review of the literature on the cost-effectiveness of adherence-enhancing interventions with regard to treatment of acute and chronic diseases; and, an economic model, based on evidence from a systematic review of the literature, designed to estimate the cost-effectiveness of adherence-enhancing interventions in relation to antibiotics for adults with upper respiratory tract infections.

The review of the economics literature over the past 30 years shows a paucity of evidence on the cost-effectiveness of adherence-enhancing interventions. Very few studies were identified that were full economic evaluations. The review concluded that evidence on the cost-effectiveness of adherence-enhancing interventions is of insufficient quality and quantity to inform healthcare decision makers. Further economic assessments are required to inform policy decisions.

A systematic review of the clinical effectiveness of interventions aimed at improving adherence to antibiotics for the management of upper respiratory tract infection identified two, well conducted, randomised controlled trials. The interventions - education (verbal and written information) and a combination of education and behavioural counselling (verbal and telephone back-up) - were shown to be effective in improving medication adherence.

A decision analytic economic model, populated with data from the review and other secondary sources, was designed to assess the cost-effectiveness of these two interventions. Following current best practice guidelines for the management of upper respiratory tract infection in the UK primary care setting, the addition of verbal and written information regarding adherence during general practitioner consultations was cost-effective for both immediate and delayed prescribing strategies. These results, however, should be interpreted with caution, as they are highly sensitive to small changes in parameter estimates.

7.2 Introduction

Non-adherence to appropriately prescribed medicines is recognised as one of the major factors contributing to therapeutic partial or non-response (1,2). It is highly prevalent, and presents a significant barrier to the safe, effective and cost-effective use of medicines. There are numerous interventions aimed at improving adherence to medications and are of varying efficacy. These have been reviewed extensively (see chapter 6). However the decision as to whether an effective adherence-enhancing intervention is to be implemented in routine clinical practice also requires consideration of its cost-effectiveness. Interventions that are not deemed to be cost-effective are less likely to be reimbursed by payers of healthcare and/or delivered by healthcare providers than those that represent good value for money. A previous review, however, has indicated that the evidence-base relating to the economics of adherence-enhancing interventions is sparse and generally of poor quality (3). Healthcare providers are consequently faced with uncertainties when making informed decisions on the availability of interventions to promote better medication adherence. Adherence research is focused mainly in chronic disease management (see Chapters 4) yet it is of interest to consider adherence to acute conditions that require full adherence to a short-course of treatment and can be targeted with relative simple, effective interventions in a routine primary care setting.

7.3 Aims and objectives

The aim of this work package was to generate economic evidence to inform policy and practice about adherence-enhancing interventions. The objectives were:-

- To update reviews of the literature associated with the cost-effectiveness of adherence-enhancing interventions.
- To estimate the economic impact of adherence-enhancing interventions using a decision analytic model populated by data from the literature review and other secondary sources.

In order to achieve these objectives, the following activities were planned:-

- A systematic review of the literature on costs and cost-effectiveness of adherence-enhancing interventions with regard to treatment of acute and chronic diseases.
- Modelling the cost-effectiveness of adherence-enhancing interventions in the case of prescribing of antibiotics for upper respiratory tract infections in adults in primary care.

The report is in two parts: firstly we report on the literature regarding costs and cost-effectiveness of adherence interventions; secondly on the subsequent de novo economic evaluation.

7.4 Part 1: Systematic review of economic evaluations

7.4.1 Method

We identified two systematic reviews of the cost-effectiveness of adherence-enhancing interventions which were published prior to the commencement of work package six. Elliott et al. (2005) (3) published a review that was later updated by the National Institute for Health and Clinical Excellence (NICE) (2009) (4); consequently the ABC project updated the latter.

The updated review (2009-2010) follows the PRISMA guideline on best practice for the reporting of systematic reviews (5).

7.4.2 Protocol and registration

The protocol was designed to be consistent with the review of Elliott (2005) (3), and the subsequent review by NICE.

7.4.3 Eligibility criteria

Intervention: Any intervention or change in practice, systems, or method of healthcare delivery, described as being intended to increase the adherence to (including persistence with) medications. *Types of studies:* Economic evaluation published as full articles in peer reviewed publication. *Types of participants:* All human: prescribed medication for any condition. *Types of outcome measures:* To be included in the review the study had to report an incremental cost-effectiveness analysis. *Exclusion criteria:* Letters and editorials were excluded. Assessments of non-pharmaceutical products (including vaccines) were excluded. No language restrictions were imposed.

7.4.4 Information sources

References published in peer reviewed journals between 01/01/2009 and 31/12/2010 were identified by searching electronic databases. The search was applied to MEDLINE (Ovid), CINAHL (EBSCO), EMBASE (Ovid) and PsycINFO (Ovid).

7.4.5 Search

The search strategies for each database are detailed in appendix 7.1. For consistency within the ABC project, the search strategies used to identify adherence papers in work package one (taxonomy and terminology of patient adherence) were used in this work package (6). The search terms for adherence were coded according to the indexing system specific to each database. “MeSH terms” were used in MEDLINE and the “EMTREE tools” were used in EMBASE.

7.4.6 Study selection

Eligibility assessment of the title and abstract was performed independently in an un-blinded, standardised manner by a single reviewer (DH), using pre-defined inclusion and exclusion criteria.

7.4.7 Data collection process and items extracted

Full text articles of publications eligible for inclusion were retrieved, and the following data were extracted: Description of the intervention, medicine(s) and population; overview of the methods employed for assessment of efficacy and determination of cost-effectiveness and costing perspective; summary of the cost, effectiveness and economic results; and comment on the uncertainty associated with the main outcome, and the study authors' main conclusion.

7.4.8 Risk of bias in individual studies

Bias refers to systematic deviations from the true underlying effect that may be attributable to poor study design, or data collection, analysis and interpretation procedures. Our protocol for bias assessment was to asses study deviations from standard good methodological practice, namely the Drummond checklist (7). This standardised instrument for critical appraisal poses questions relating to: appropriateness of the economic question being asked, comprehensiveness of the description of the intervention(s), robustness of evidence on effectiveness, comprehensiveness of resource use identification and cost consequences, valuation of costs and outcomes, adjustment for differential timing, application of an incremental analysis, consideration of uncertainty, and adequacy of data presentation and analysis.

7.4.9 Study selection

The search of electronic databases identified 719 potentially relevant studies, after electronic de-duplication using RefWorks[1]. 663 publications were excluded following initial screen of title and abstract. 56 full-text papers were sought, 51 were excluded on the basis of the exclusion criteria or not meeting the inclusion criteria (e.g. a cost analysis, not an economic analysis). The remaining five papers were assessed to eliminate those concerned with immunization, or with impact of (non)-adherence on cost-effectiveness, or that were not full economic evaluations.

No papers were identified by the search. See PRISMA (5) flow diagram in figure 7.1 for a full breakdown of study selection.

[1] ProQuest LLC (2010) http://www.refworks.com/

7.5 Results

Between January 1980 and April 2004 Elliott et al. (2005) (3) identified 45 comparative studies; 33 educational interventions, 20 with multiple components. Interventions reported in twenty-three studies were not linked to proven reasons for non-adherence. Reporting of outcomes related to non-adherence was often unclear. Cost data were of poorer quality than outcomes data, using average or estimated costs and omitting some important cost elements. Nine studies carried out an incremental analysis, but Elliott et al. (2005) (3) reported that none of the studies met all minimum requirements for an economic evaluation of an adherence-enhancing intervention. As such they concluded "We were not able to make definitive conclusions about the cost-effectiveness of adherence-enhancing interventions due to the heterogeneity of the studies found and incomplete reporting of results."

The findings of the 2009 NICE update of the systematic review by Elliott (2005) (3) are summarised in table 1. The report concluded that "there is a clear need for more and better research ... to assess the potential of interventions to increase adherence to improve healthcare outcomes and/ or reduce healthcare costs".

As no further studies have been identified, the results remain consistent with those reported by NICE in 2009 (see table 1).

7.6 Conclusion of updated review

Evidence on the cost-effectiveness of adherence-enhancing interventions is of insufficient quality and quantity to inform healthcare decision makers.

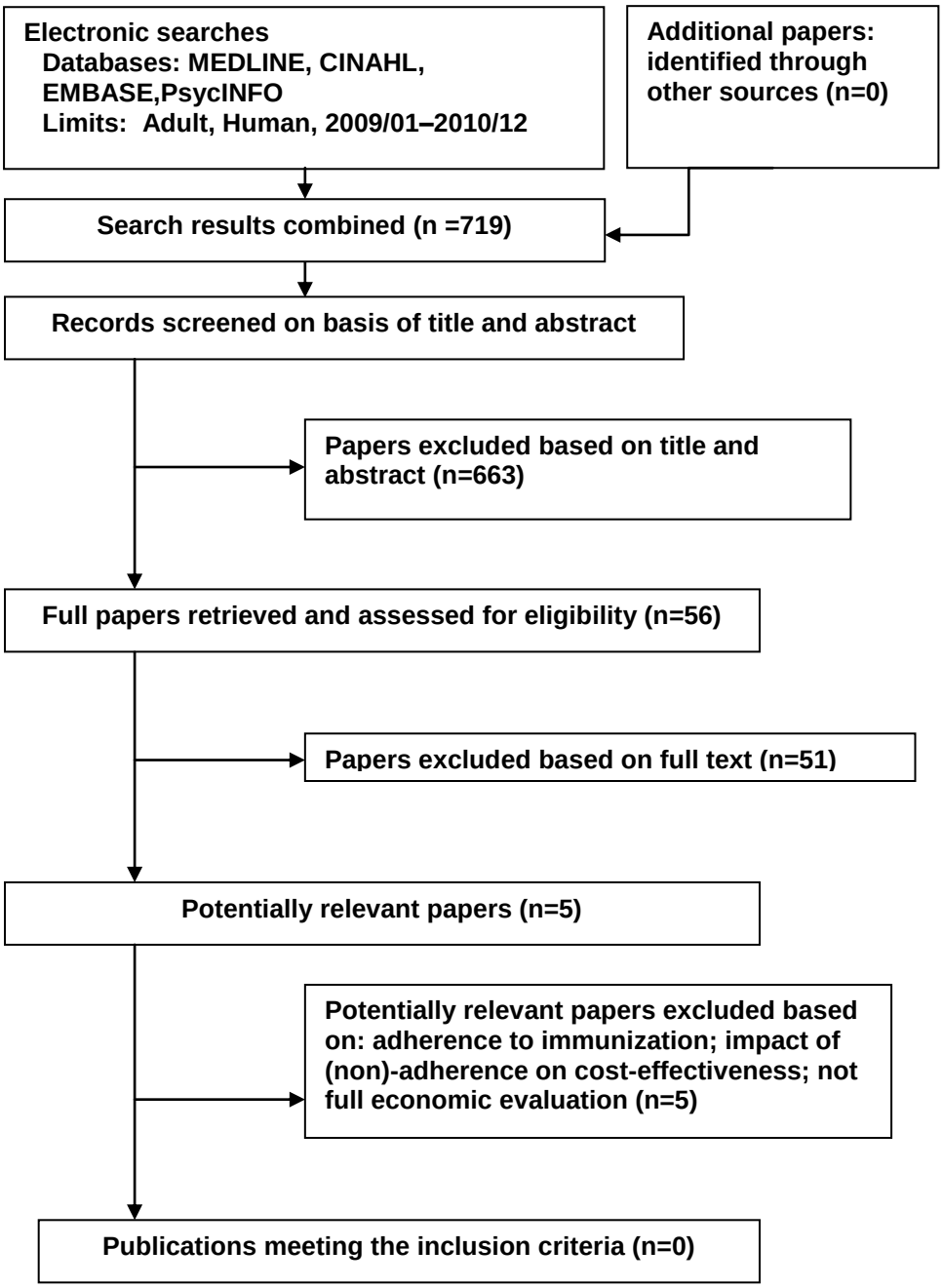


Figure 7.1: Flow diagram of study selection

Table 7.1: Summary of findings of NICE (2009) (4)

Intervention	Medicine	Population	Method	Perspective	Cost results
Bosmans et al. (2007)(8) Pharmacist led education and coaching intervention (3 personal contacts, 1 take home video) plus standard care	Antidepressants	Adults with 'new episode (not used antidepressant in previous six month period)' prescription for non-tricyclic antidepressant from GP for depressive complaints	RCT of 151 patients; Primary outcome MEMS; 6-months follow-up	The Netherlands, societal (€, 2002 values)	Mean total costs were €3275 in the intervention group and €2961 in the control group.
Brunenberg et al. (2007) (9) MEMS monitoring system plus adherence training	Antihypertensives	Systolic BP >160mm Hg and/or diastolic BP>95mm Hg despite use of antihypertensive drug	RCT of 253 patients; Primary outcome measure <85% days taking the prescribed dose; 5-months follow-up	The Netherlands, healthcare and societal perspective(€, 2002 values)	Total direct healthcare costs were €827 and €927 in the intervention and control groups, respectively. Total costs, including all direct and indirect costs, were €1573 and €1526, respectively
Edwards et al. (2005) (10) Long acting injection vs. oral	Risperidone	Community-dwelling patients with schizophrenia who had previously suffered a relapse requiring hospitalization	Decision analysis over a 1-year time horizon	Healthcare payers in the United States ($, 2003 values)	Using long acting risperidone rather than an oral atypical antipsychotic agent is predicted to result in US$161 of healthcare savings per patient per year compared with oral risperidone.

Table 7.1: Summary of findings of NICE (2009) (4) [continued]

Effectiveness results	Economic results	Uncertainty	Authors' conclusion
Bosmans et al. (2007)(8) Mean adherence did not differ significantly between the intervention group (88%) and the control group (86%) at six months (mean difference 2.1%, 95% CI -5.6, 9.8)	The ICER for coaching and education by pharmacists compared with usual care was €149 per 1% improvement in adherence and €2550 per point improvement in the Hopkins Symptom Checklist depression mean item score.	Uncertainty was considerable. Costs and effects were distributed in all four quadrants of the cost effectiveness plane	Cost-effectiveness planes and acceptability curves indicated that the pharmacist intervention was not likely to be cost effective compared with usual care
Brunenberg et al. (2007) (9) At 5 months, 53.7% of MEMS patients had normalised BP compared to 50.6% in usual care (difference +3.1%; 95%CI -9.7 to 15.8). An incremental 0.003 QALYs were generated (95%CI -0.005 to 0.01) in the experimental arm	ICER €15,667 per QALY gained	Univariate sensitivity analysis revealed considerable uncertainty. The probability of cost effectiveness was around 77%	Patients may benefit from the use of a MEMS monitor in situations where BP targets are not reached because of suspected non-adherence and both patient and GP are reluctant to increase the dose or number of antihypertensive drugs
Edwards et al. (2005) (10) On long acting risperidone, 26% of patients are predicted to experience relapse requiring hospitalisation and 24% relapse not requiring hospitalisation. However, the analysts assumed 20% increase in adherence would result in 3.1 point increase in PANSS	Long-acting risperidone is predicted to be more effective and also less costly than its comparators	Univariate sensitivity analysis reported to have been robust. However, at the upper bound of the 95%CI for relapse rates requiring hospitalisation there was an incremental cost for long acting risperidone of US$821per days of hospitalisation averted compared to oral risperidone	Long-acting risperidone may be a cost saving therapeutic option for patients with schizophrenia

7.7 Part 2: Systematic review and economic evaluation of interventions to improve adherence to antibiotics for upper respiratory tract infections.

Upper respiratory tract infections (URTI) are common. Although consultation rates for URTI have declined in the 10 years prior to 2006, they remain the most common acute illness treated in primary care (11). The guidance on URTI issued by NICE states that 60% of all antibiotic prescribing is to treat RTI (12). However research suggests that antibiotic treatment is of limited effect when used in the treatment of URTI (13). Antibiotic prescribing should be limited to the patients who are most likely to benefit, and are usually only given if the infection is likely to be bacterial (12). Poor adherence to the dosing regimen has been linked to both treatment failure and development of antibiotic-resistant bacteria (14, 15, 16, 17).

Ensuring adequate adherence to antibiotic medication is important when antibiotic prescribing is indicated i.e. when the risks of complications of bacterial origin are present. A number of interventions for the management of adherence to chronic therapies have been developed and assessed for their efficacy (18, 19). However, there is a paucity of information on the effectiveness of interventions to enhance adherence to acute treatments, despite the prevalence of sub-optimal adherence to such treatments (20). Moreover, there are no economic evaluations, to our knowledge, of interventions designed to improve adherence to antibiotic therapy in URTI.

7.8 Aims and Objectives

The purpose of this systematic review and economic evaluations is to take a disease-specific approach, focusing on studies that evaluate interventions designed to improve adherence in patients treated with antibiotics for acute URTI, and to develop an economic model to assess the cost-effectiveness of the interventions.

7.9 Methods

A protocol was developed according to the procedures outlined in the Cochrane Handbook (21) and reporting follows the PRISMA reporting guidance (5).

7.9.1 Eligibility criteria

Criteria for inclusion in the review were: (i) adults ≥18 years of age, prescribed an antibiotic treatment for an acute upper respiratory tract infection; (ii) adherence to the antibiotic treatment was measured; and (iii) an intervention was implemented, with a comparator, which aimed to improve patients' adherence to antibiotic treatment. All study designs were considered, with no limits on length of follow-up or language.

Studies were excluded if the participants were <18 years old, if participants had chronic or lower respiratory tract infections, including tuberculosis, or if 2 different antibiotics were being compared. Children were excluded because they do not have control over their medication, thus focusing on the parent, not the child. Chronic URTI conditions were excluded because they are inherently more complex than acute infections, have the likelihood of patients' taking concurrent medications, and incur the increased likelihood of microbial resistance. Studies were excluded if the intervention was intended to improve prescriber's adherence with prescribing guidelines.

7.9.2 Information sources

Comprehensive searches for published literature were conducted in 5 electronic databases: Medline including Medline First Process, CINAHL, EMBASE, PsychInfo and Cochrane. The searches were from database inception to 8th March 2011.

7.9.3 Search

The search was designed to identify studies of patients with a diagnosis of acute respiratory disease, in which adherence to antibiotics was measured, and interventions to improve adherence to antibiotic treatment were tested. The search was a combination of keywords and MeSH terms describing each component; for 'disease' we included respiratory tract infection, syncytial virus, tonsillitis, larynx, pneumonia; for 'adherence' we included patient adherence, treatment refusal, adherence, and combinations thereof. For 'intervention', we used directly observed therapy, health education, reminder systems, electronic mail, telephone, nurses, pharmacists, physicians, dose regimen, dose frequency; for 'medication', we used antibiotics, anti bacterial agents as well as the relevant drug names. Filters identified RCTs and observational studies. The syntax varied between databases. References were checked for any additional papers, including the recent systematic review of Interventions designed to improve adherence to antibiotics irrespective of disease (18).

7.9.4 Study selection

Titles and abstracts of all identified studies were reviewed independently by 3 unmasked reviewers (SB, DH & PL) for relevance with the inclusion criteria. All potentially relevant papers were obtained. The papers were independently reviewed by the same reviewers. Any disagreements were resolved by consensus.

7.9.5 Data collection process

SB extracted the data using a pre-prepared data extraction form; extractions were checked by PL and DH. Data extraction was based on sample characteristics including disease and treatment and sample size, study characteristics, intervention and control details, inclusion/exclusion information,

location, adherence-related outcomes, methods used to measure adherence, outcomes and statistical analysis.

7.9.6 Data items

Data were extracted on the following components: Study funding, setting and design; characteristics of study participants, antibiotics prescribed, subgroups defined for analysis, nature of the intervention and the control groups, outcome measures and principal findings (results).

7.9.7 Risk of bias

The study quality was conducted independently by 2 reviewers (SB and PL) using Jadad (22) scoring system (0-5, allocation concealment A-C). In addition, a framework specifically designed to critique adherence research was employed (23). This tool provides an objective assessment of the rigour of the prospective adherence studies (23) (scoring 0-22) (Appendices 7.22 & 7.3). Any disagreements in the data review process were resolved by consensus.

7.10 Results

7.10.1 Study selection and flow diagram

We identified 2,009 potential papers from our searches of 5 databases plus a further 13 from authors. 525 duplicates were removed. 1,497 titles and abstracts were screened for inclusion in the review, 1436 were excluded. 61 full papers were obtained for more detailed review, 59 were excluded, detailed by the flow chart in figure 2. No further papers were found after reviewing the abstracts of the potentially relevant papers, including a recent systematic review of medication adherence interventions irrespective of disease (18).

7.10.2 Study characteristics – method, participants, intervention, outcomes

Two studies met the inclusion criteria for this review, both were randomised controlled trials; Urien et al. 2004 (24) and Segador et al. 2005 (25). Both studies were conducted in Spain and recruited patients with acute sore throats or a diagnosis of tonsillitis/pharyngitis. Patients in both studies were prescribed a 10-day course of penicillins, the interval between doses was either eight hours (amoxicillin) (24) or six hours (phenoxymethylpenicillin) (25). The duration of the studies was 10-12 days. Table 7.2 summarises the studies.

The studies identified examined the influence of an educational intervention (25), and of a combined education and behavioural / counselling intervention (24). In both cases the intervention was compared to verbal instruction alone, on adherence to antibiotic treatment for acute upper respiratory tract infections. The methods of delivering the intervention were different; in addition to

verbal instruction, Urien (24) included a reminder phone call 4 days after delivery of the prescription, whereas Segador (25) included written as well as verbal instructions on the first day of treatment. The control groups were given the same verbal instructions as the intervention groups, but were fully described only by Urien (24).

The patient populations in these two studies were similar in terms of age and sex. Both studies excluded patients to whom the intervention could not be delivered (patients without a phone in Urien (24), and illiterate patients in Segador (25)). Desired sample sizes were calculated for both studies, and these numbers were met (24) or exceeded (25). Urien (24) allowed for expected losses to follow up in their planned sample size. Intention to treat analyses were performed in both studies, although for Urien (24) this took the form of a worst case scenario analysis. The losses to follow up were fewer than allowed for in the sample size calculation (24). Two of these losses were due to lack of a telephone, but reasons are not given for loss of the other five patients. All included patients were followed up in Segador (25).

Adherence was measured by pill count between days 9 and 12 after the prescription was delivered. Participants were not told in advance that a pill count would be included in the visit. Reasons for non-adherence to medication were collected by interviewer; in addition Urien (24) reported patient self assessment of adherence.

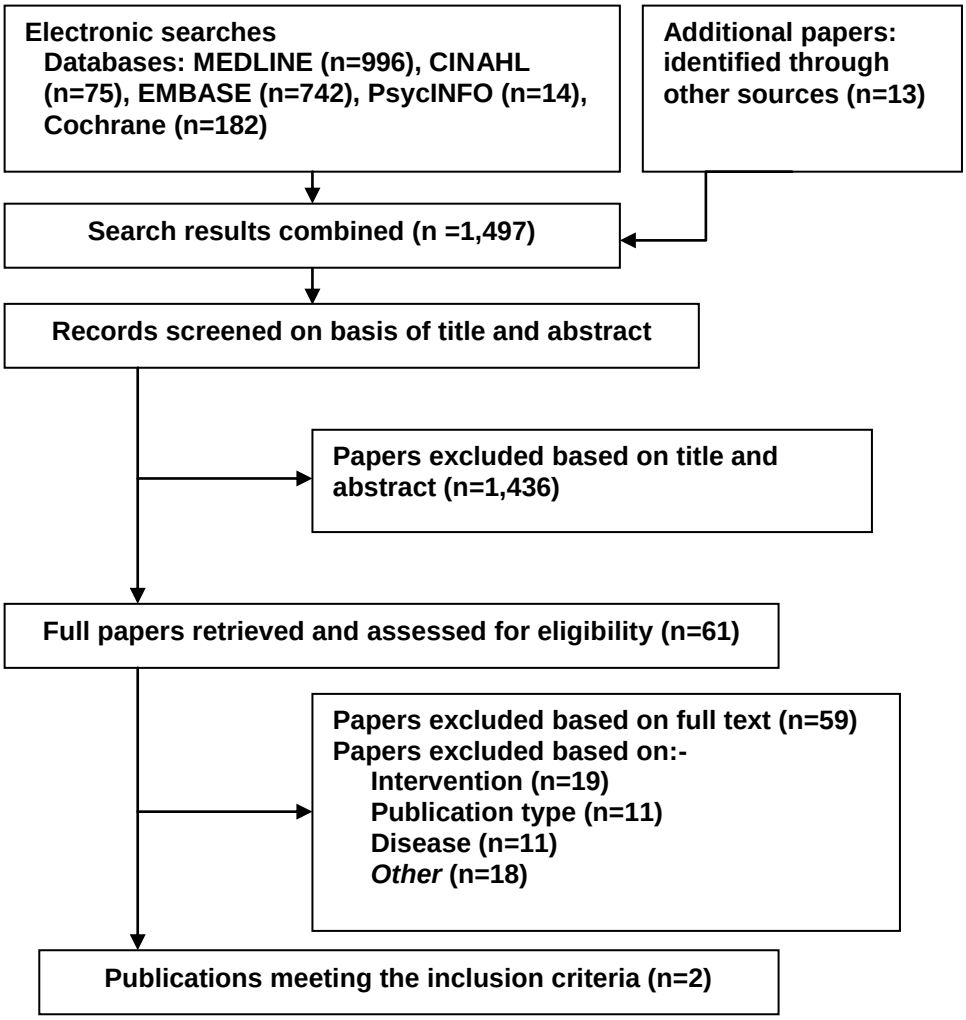


Figure 7.2: Flow diagram of study selection [review 2]

7.11 Risk of bias within individual studies

Neither study was of high quality as measured by the Jadad score (22), this being 3a for Segador (25) and 2b for Urien (24). Using the Adherence Assessment Score, Segador (25) again scored more highly, with 18 and Urien (24) with 14 (23). Appendices 7.2 & 7.3 report these assessments.

Both studies were parallel group, randomised controlled trials (RCTs) (24),(25). The randomisation technique is not described by Urien (24), but Segador (25) report using a computer generated randomisation sequence implemented with numbered containers. Urien (24) masked participants to the purpose of the study and to their treatment group. Segador (25) note that the statistician was masked to treatment allocation.

Potential for bias in the results from those of the general population could result from either the exclusion criteria in Urien (24) or the trial population in Segador (25). Urien (24) stated imprecisely that patients "belonging to any group that, according to the doctor's opinion, would make monitoring difficult". These types of patients would be present in practice, and might include those in greater need of some intervention to improve their adherence. Urien (24) made an effort to describe patient characteristics such as education and occupation that might affect adherence, and these did not appear to be unusual. All of the patients in Segador study (25) were attending a student health service; this differentiates them from the general population. Comparability across treatment arms was achieved in both studies.

Neither study described standard or usual care, leaving it unclear whether the studies were comparisons of 2 interventions or whether the control group represented usual care.

Both studies relied on pill count as the measure of adherence. This method is susceptible to bias (through, for instance, 'pill dumping') (26) however the researchers reduced the risk of bias by unannounced visits with no prior explanation about adherence measurement.

7.12 Results of individual studies

7.12.1 Pill count adherence

Both studies found a higher proportion of adherence, determined by the quantity of remaining doses, in the intervention group than the control group, although for Urien (24) this difference was only significant in the analysis of evaluable patients (p=0.005). For these patients, 78% in the intervention group were deemed to be adherent (<80% or >110% of doses presumed to be taken based on untaken doses) compared with 54% in the control group. In the worst case, scenario analysis there was still a higher proportion of adherent patients in the intervention group (73%) than the control group (56%) (p=0.042). The proportion of adherent patients in Segador (25) was 66% of the intervention group and 54% of the control group and when patients were classified as adherent,

under-adherent (>80%) or over-adherent (<100%) there was a significant difference between treatment arms (p=0.0008). Fewer patients in the intervention group of Segador (25) were under-adherent (intervention 15%, control 39%), but there were a higher proportion of over-adherent patients in the intervention group (19%) than in the control group (6%). These results, however, should be interpreted with caution given the methods of adherence measurement employed.

The mean overall adherence was similar in both studies, 84% (n=20) and 87% (n=25). Urien (24) noted that the average adherence was higher in the intervention group but values were not provided. Segador (25) reported the mean adherence for each treatment arm, which was higher in the intervention group (94%) than in the control group (81%). This difference was statistically significant (p <0.05).

Both included studies calculated indicators of clinical relevance: absolute risk reduction (ARR), relative risk reduction (RRR) and number needed to treat (NNT), see Table 2. The number of patients to which the interventions would need to be delivered in order to avoid one non-adherent patient was 5.85 in Urien (24) and 8.77 in Segador (25).

7.12.2 Patient-reported adherence

Urien (24) recorded patient-reported adherence and compared this to adherence measured using the pill count method. This analysis illustrates the differences between patient-reported and pill-count adherence measures. 83% of patients reported themselves as adherent. According to the pill count 67% of the patients included in this analysis had adhered with treatment. Five (4%) patients reported they had been non-adherent when the pill count indicated they were adherent. Conversely, 25 (21%) patients reported themselves as adherent but were non-adherent according to the pill count.

The validation analysis of patient-reported adherence by pill-count adherence found a sensitivity of 35% and a specificity of 94%. There was a positive probability quotient of 6 and a negative probability quotient of 0.67. This analysis assumed that pill-count could be regarded as the standard.

7.12.3 Reasons for early discontinuation

Urien (24) report reasons for early discontinuation of medication given by 33 patients, 10 of whom were classified as adherent according to the pill count. Segador (25) report the reasons of 76 patients who discontinued early. Subjective cure and oversight were the most commonly given reasons for early discontinuation in both studies. There was a higher proportion due to subjective cure in Segador (25) (57%) than Urien (24) (33%).

Significantly more patients reported early discontinuation due to subjective cure in the control group of Segador (25) than in the intervention group (p=0.0001). Six percent of patients in the intervention group discontinued early due to distrust, but no patients in the intervention group gave distrust of

treatment as a reason. Segador (25) note that one patient in the intervention group answered “side effects” but then qualified this by saying they did not collect their prescription from the pharmacy because they had previously experience adverse effects with the medication. One patient in the control group discontinued due to distrust of the treatment never collected the medication from the pharmacy.

7.12.4 Clinical outcome

Urien (24) evaluated the outcome of the treatment with a physical examination of the pharynx to check for inflammation at the follow-up visit. The majority of patients had normal examinations, with a slightly higher number of patients in the control group than the intervention group appearing cured. The results are similar to the patient-reported cures. There was no significant difference between treatment groups (p=0.576).

7.12.5 Patient reported cure

Both studies asked patients whether they thought they were cured. The majority of patients, regardless of treatment group, in each study felt better, although more patients in Urien (24) reported a cure than in Segador (87% versus 61%). Otherwise, there was little difference between groups, with more patients in the control group than the intervention group reporting a cure, but the reverse was reported in Segador (25).

Table 7.2: Summary of included trials of educational interventions to improve adherence in acute respiratory tract infections

Study and setting	Participants	Subgroups analysed	Interventions	Quality judgment	Outcome measures	Results (n=)
Urien 2004 (24) Single centre in Alicante, Spain. Funder not reported **Study type (duration):** Open label, parallel-group randomised controlled trial (10 days)	Patients >18yrs with diagnosis of tonsillitis/pharyngitis and prescribed amoxicillin 500mg, 750mg or 1g tid for 10 days Rad64/64	Adherent (80-110%) and non-adherent (<80% 0r >110%) Cured vs non-cured (clinical improvement) Physical examination (normal vs. altered) Losses to FU assumed all losses in I non-adherent and all in C adherent (ITT)	Intervention: **Education (verbal) and behavioural / counselling (telephone back-up).** Verbal education plus reminder phone call on 4th day of treatment providing more information about the importance of adherence and the risks of early treatment discontinuation. Control: Verbal education, with no reminder.	Sequence generation unclear (not described), allocation concealment adequate, blinding inadequate (unblinded). Jadad score 2(b), Adherence score 14, Meta-anal GRADE assessment: RCT therefore high, with limitations re randomisation and blinding, also usual care is not described therefore the control may be different from normal practice.	ITT analysis - Pill count ; (80-110% vs.<80% or >110% Clinical indicators of adherence ARR, RRR and NNT Not including losses to FU Pill count ; (80-110% vs.<80% or >110% Clinical indicators of adherence ARR, RRR and NNT Self reported adherence using Haynes-Sacket, Self reported reasons for non-adherence, cured side-effects oversight distrust of treatment other Patient reported cure, Clinical cure (GP physical exam)	I=73%(47)C=56%(36)*p=0.042* I=27%(17) C=44%(28) ARR 17.1 RRR 39.1 NNT 5.85 I=78% (47)C=54%(33)*p=0.005** I=22%(13) C=46%(28) ARR 24.2 RRR 52.7 NNT 4.13 Validation of reported adherence found a positive probability quotient of 6 vs. negative probability 0.67. I=25% (3) C=38% (8), I=8% (1) C=24% (5), I=33% (4) C=19% (4), I=25% (3) C=5% (1), I=8% (1) C=14%(3) I=85%(51), C=88%(54) I=82%(49) C=92%(56)

Table 7.2 [continued]: Summary of included trials of educational interventions to improve adherence in acute respiratory tract infections

Study and setting	Participants	Subgroups analysed	Interventions	Quality judgment	Outcome measures	Results
Segador, 2005 (25) Multi centre in Ibiza, Spain (n=7) Funder not reported **Study type (duration):** Open label, parallel-group randomised controlled trial (12 days)	Patients >18, literate, with acute sore throat for <7days requiring antibiotics in GPs opinion. Prescribed 250mg of oral penicillin V or G 4 per day for 10 days. Erythromycin if allergic to penicillin 79/79	Adherent (80-110%) and non-adherent (<80% 0r >110%) Under and over adherence, Patient reported cure	Intervention: **Education (verbal & written)** Verbal and written information on day of treatment re. importance of adherence and risks of early discontinuation. Control: Verbal information as above, no written info. No mention of usual care	Randomisation clearly described, allocation concealment adequate, blinding adequate. Jadad score 3(a), Adherence score 18, Meta anal GRADE assessment: usual care is not described therefore the control may be different from normal practice.	Pill count ; (80-110% vs. <80% or >110% Under adherent <80% Over adherent >110% Clinical indicators of adherence ARR, RRR and NNT Self reported reasons for non-adherence, Cured side-effects oversight distrust	I=66% (52) C=54% (43) I=34%(27) C=46%(36) I=15% (12) C=39%(31) I=19% (15) C=6%(5) ARR 14 RRR 24.9 NNT 8.77 I=40% (10) C=65% (33), I=12% (3) C=6% (3), I=48% (12) C=23% (12), I=0 C=6% (3),

*Sig.dif *p=0.05 (no other significant differences in either study)*

7.13 Economic evaluation of intervention to improve adherence to antibiotics for the management of acute upper respiratory tract infections in adults: overview

The economic analysis modelled the clinical pathways recommended in the clinical guideline produced by the UK National Institute for Clinical Excellence (NICE) for prescribing of antibiotics for self-limiting respiratory tract infections in adults in primary care (12).

The guideline recommends a *no antibiotic* or *delayed antibiotic* prescribing strategy for patients with the following conditions:-

- acute otitis media
- acute sore throat / acute pharyngitis / acute tonsillitis
- common cold
- acute rhinosinusitis
- acute cough / acute bronchitis

NICE (2008) (12) recommends that a delayed prescription with instructions for the patient, can either be given to the patient or left at an agreed location to be collection at a later date.

Immediate antibiotic prescribing depends on clinical assessment of severity and is recommended for treatment of acute sore throat / acute pharyngitis / acute tonsillitis when three of more criteria are present:-

- presence of tonsilliar exudate
- tender anterior cervical lympadenopathy or lymphadentitis
- history of fever
- absence of cough

The model developed to support the NICE guideline provided the basis for the current economic analysis but was modified by (i) using more recent secondary sources of evidence; (ii) use of different clinical assumptions; (iii) the incorporation of interventions to improve adherence. The decision analytic model estimated the cost-effectiveness of immediate or delayed prescribing strategies alone versus immediate or delayed prescribing strategy with interventions designed to increased adherence to antibiotic prescription. Two adherence-enhancing interventions were considered: (i) verbal and written information on the day of consultation, regarding the importance of adherence and risks of early discontinuation, versus, verbal education alone, based on Segador (25); and, (ii) verbal education plus a reminder phone call on the fourth day of treatment providing more information about the importance of adherence and the risks of early discontinuation, versus verbal education alone, with no reminder as in Urien (24).

The model provides an estimate of costs and health outcomes in terms of quality-adjusted life years (QALYs). The costing perspective was that of the UK National Health Service (NHS) and Personal

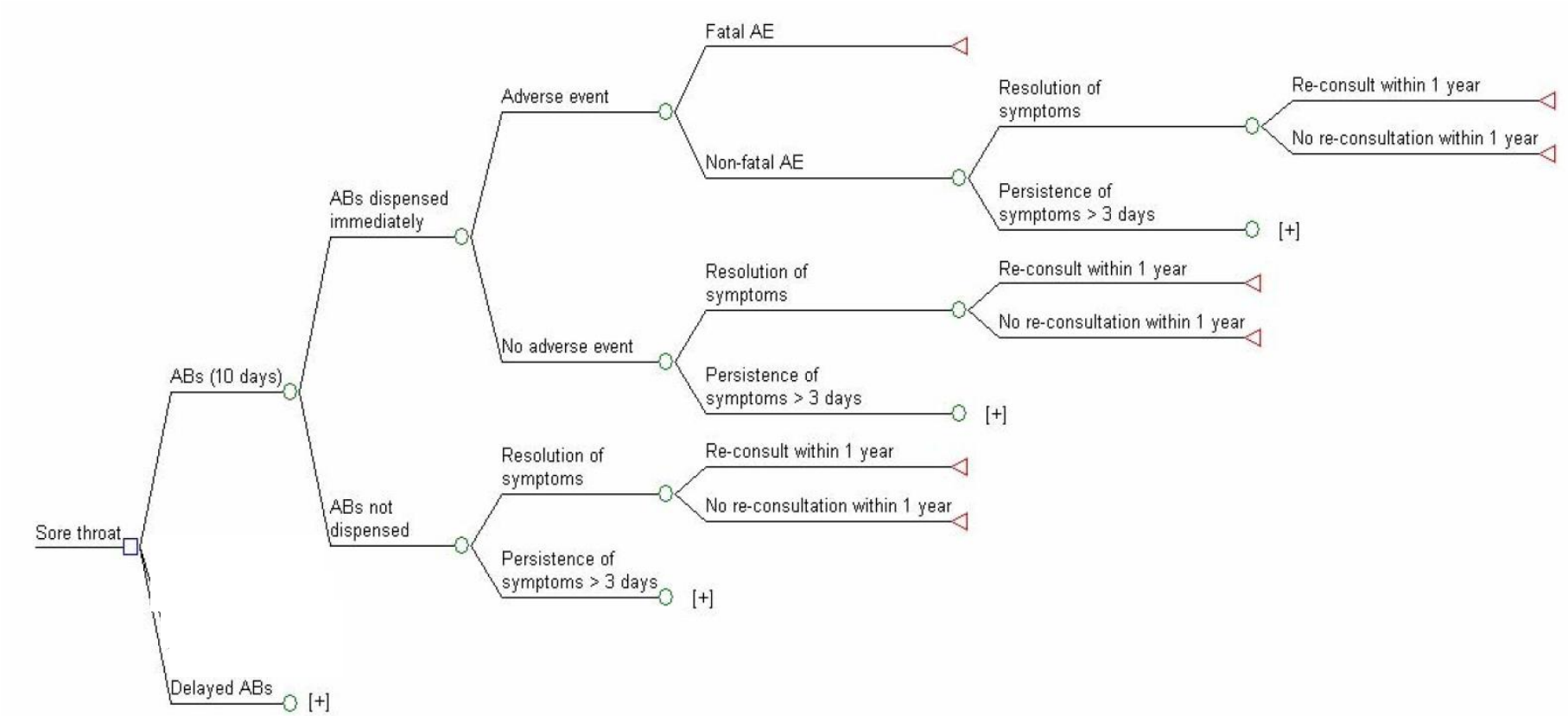
Social Services, with a price year of 2009-10. The analysis adopted a 1-year time horizon. One-way sensitivity analyses were used to explore the contribution of individual parameters to overall uncertainty in the cost-effectiveness of the adherence-enhancing interventions. The decision analytic model was developed in Microsoft Excel.

7.14 Comparators

In the model, patients were assigned to one of the following strategies:-

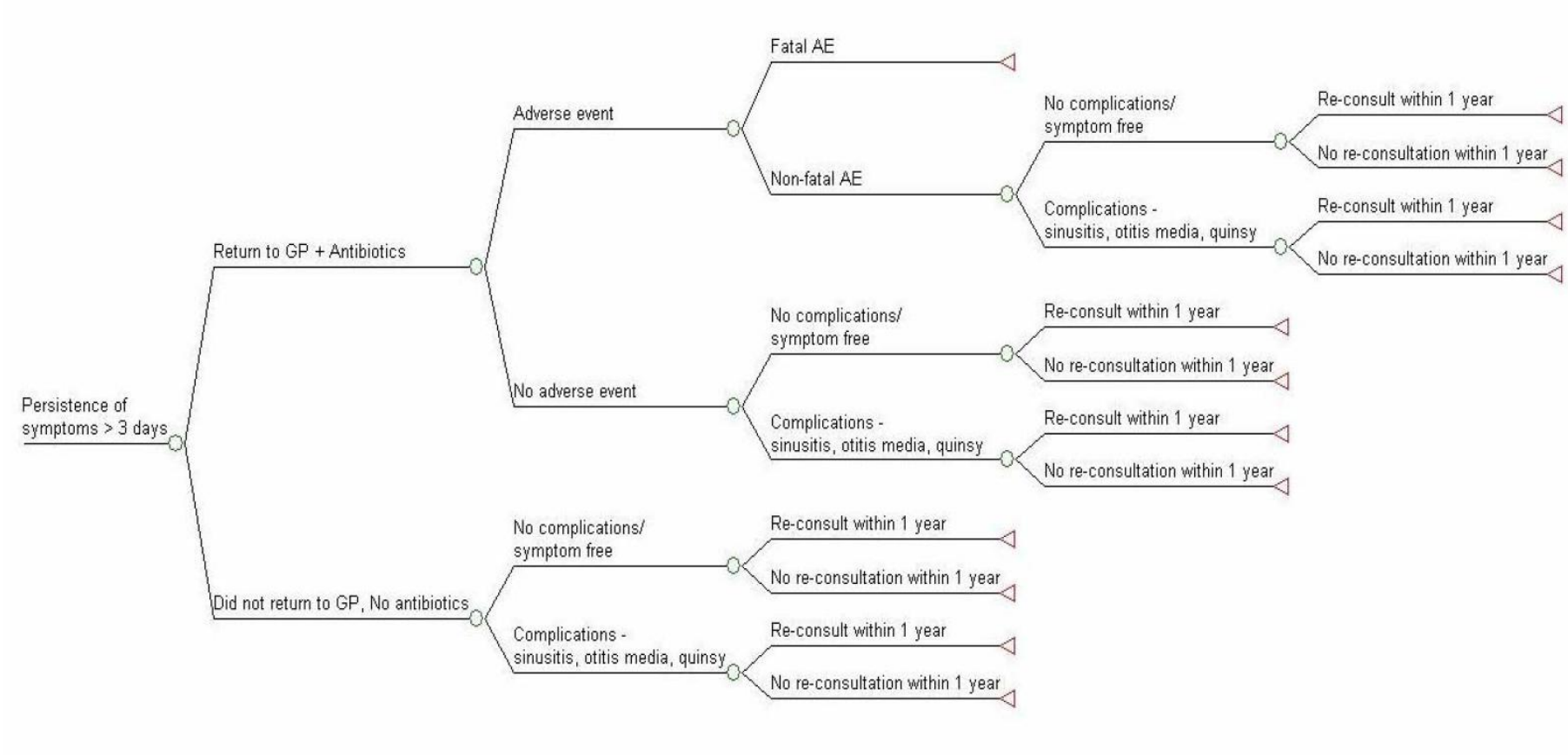
- Strategy 1: immediate prescription for antibiotics
- Strategy 2: immediate prescription for antibiotics + adherence-enhancing intervention
- Strategy 3: delayed antibiotics
- Strategy 4: delayed antibiotics + adherence-enhancing intervention

A diagrammatic representation of the model is given in figure 7.3. If patients had persistent symptoms for more than 3 days, they then followed the pathway shown in figure 7.4. The probability of resolution of symptoms varied according to each strategy.



ABs – antibiotics, AE – adverse event

Figure 7.3: Diagrammatic representation of the decision tree (NICE 2008, (12))



AE – adverse event

Figure 7.4: Diagrammatic representation of the decision sub tree (NICE 2008, (12))

7.15 Model inputs

7.15.1 Probability and treatment effects

Tables 7.3-7.5 present the probabilities and individual parameter estimates used in the model.

7.15.2 Probability of receiving antibiotics

The probability of receiving antibiotics were taken from an open-label, randomised controlled trial by Little et al. (1997) (27) of immediate, delayed and no antibiotic strategies in UK primary care; in which 99% of patients in the immediate arm, and 31% of patients in the delayed arm, were given a prescription and had their prescription dispensed from a pharmacy. The base case analysis adopts the same approach as NICE (2008) (12) with all patients in the immediate arm having their prescription dispensed. The same caveat applies, that this assumption may slightly overestimate the costs in the immediate antibiotics arm.

7.15.3 Resolution of symptoms

The probability that patients' symptoms persist for more than 3 days is taken from Little et al. (1997) (27). Patients with unresolved symptoms could return to the GP and receive a further prescription for antibiotics, and, if they did return, they would receive further antibiotics (NICE Guideline Development Group (NICE 2008) (12)). Data on re-attendance were taken from Little et al. (1997) (27); these data were based on re-attendance within one month – but it is acknowledged that the time frame of the illness would be shorter than one month. The likelihood of treatment success (clinical cure assessed by general practitioner (24)) in the intervention arms was based on applying the relative risk of persistent symptoms, as derived from the systematic review described above.

Table 7.3: Summary of model parameters, values and sources, including ranges for the sensitivity analysis: antibiotics and resolution of symptoms

	Immediate antibiotics 2011			Delayed antibiotics 2011			
Parameters	**Base case**	**Lower**	**Upper**	**Base case**	**Lower**	**Upper**	**Source / comments**
Antibiotics dispensed after prescription given	1	-	0.99	0.31	-	-	Assumption: Little et al. (1997) (27) reported that some patients did not have their antibiotics dispensed or use their antibiotics in the immediate antibiotics arm (1%). This was tested in sensitivity analysis.
Resolution of symptoms in control	0.37	0.30	0.37	0.3	0.30	0.37	Little et al. (1997) (27)
Resolution of symptoms with adherence-enhancing intervention (AEI) [written]	0.47	0.30	0.47	0.41	0.30	0.47	Little et al. (1997) (27) adjusted using proportional increase in resolution of symptoms from Segador (2005) (25).
Resolution of symptoms with AEI [Telephone back-up]	0.40	0.30	0.40	0.33	0.30	0.40	Little et al. (1997) (27) adjusted using proportional increase in resolution of symptoms from Urien (2004) (24).
Resolution of symptoms with AEI	0.41	0.3	0.41	0.35	0	0.41	Meta analysis of Segador (2005) (25) & Urien (2004) (24).
Return to GP and receive antibiotics when symptoms haven't resolved	0.09	0	1	0.05	0	1	Re-consultation rates from Little et al. (1997) (31).

Table 7.4: Summary of model parameters, values and sources, including ranges for the sensitivity analysis: complications

	Immediate antibiotics 2011			Delayed antibiotics 2011			
Parameters	**Base case**	**Lower**	**Upper**	**Base case**	**Lower**	**Upper**	**Source / comments**
Overall probability of developing complications with antibiotics	0.0116	-	-	0.0116	0.0474	0.0116	Calculated from Del Mar et al. (2006) (28). This was calculated as an overall probability of developing complications (otitis media, sinusitis or quinsy). The probability of developing each complication was multiplied by the relative risk of complications, taken from Del Mar et al. (2006) (28) and added together. This manoeuvre assumes no interactions between complications. Delayed assumed to be the same as 'immediate antibiotics' in the base case. Varied in sensitivity analysis between the probability of complications when no antibiotics are given and the probability of complications when antibiotics are given.
Overall probability of developing complications with no antibiotics	0.0474	-	-	0.0474	-	-	Calculated from Del Mar et al. (2006) (28). The probabilities of having each complication were added to give an overall probability of complication. This manoeuvre assumes no interactions between complications.

Table 7.5: Summary of model parameters, values and sources, including ranges for the sensitivity analysis: adverse reactions and re-consultation

	Immediate antibiotics 2011			Delayed antibiotics 2011			
Parameters	**Base case**	**Lower**	**Upper**	**Base case**	**Lower**	**Upper**	**Source / comments**
Allergic reaction (anaphylaxis) to penicillin	0.0005	0.00025	0.001	0.0005	0.00025	0.001	British National Formulary, September 2011 (Number 62) (29)
Death due to anaphylactic shock	0.1	0.05	0.2	0.1	0.05	0.2	Neuner et al. (2003) (30)
Adverse events to switched antibiotics	0	-	-	0	-	-	Assumption (NICE 2008) (12). Adverse reactions to the antibiotics used when patients had to switch from penicillin were considered very rare, and unlikely to impact on costs according to the GDG. Therefore, to reduce complexity in the model, probability of adverse event to switched antibiotics was set to zero in the base case.
Death due to an adverse reaction caused by switched antibiotics	0	-	-	0	-	-	Assumption (NICE 2008) (12).
Re-consultation in the antibiotics strategy within a year	0.38	0	1	0.23	0	1	Little et al. (1997) (31).

7.15.4 Probability of developing complications

Complications of sore throat considered in the model were otitis media, sinusitis and quinsy. Treatment of otitis media and sinusitis was amoxicillin (500mg thrice daily for 5 days) prescribed by a GP in primary care. The treatment for quinsy was a hospital stay (1 day). Probabilities of individual complications were calculated from the Cochrane Review of developing complications of sore throat, Del Mar et al. (2006) (28).

7.15.5 Adverse consequences of antibiotics

The risk of hypersensitivity (anaphylactic) reactions was taken from the British National Formulary (September 2011, No. 62) (29) and applied to first-line treatment with penicillin. The probability of anaphylactic death was taken from Neuner et al. (2003) (30). In the base case the risk of anaphylactic reactions to a switched or second course of antibiotics was considered to be zero.

7.15.6 Re-consultation

The probability of returning to the GP with a new episode within 1 year, was again taken Little et al. (1997) (31). Little et al. (1997) (31) reported re-attendance and complications for the three strategies – data were identified for immediate and delayed prescribing.

7.15.7 Health-related quality of life weights

Table 7.6 presents the utility weights used in the model.

The disutility of sore throat, complications, and adverse reactions to antibiotics were derived from Neuner et al. (2003) (30) and subtracted from the UK population norms for EQ-5D (Kind et al 1999) (32). Utility of no sore throat was assumed to be that of the UK population norm for the EQ-5D self-rated health status 0.86. Adverse events were assumed concurrent to sore throat; whereas complications were assumed to extend the duration of ill health (disutility).

7.15.8 Costs

Tables 7.7 to 7.9 present the unit cost estimates used in the model. Unit costs of health service and resource use estimates were obtained from UK national sources, where possible (29, 33-35).

The costs of antibiotics were identified from the Drug Tariff (accessed September 2011; (33)). Prescribing regimens used to calculate the costs of antibiotics and drug treatment of complications, were taken from NICE costing report (36) and verified by clinical opinion. Patients requiring a switch of antibiotics due to unresolved symptoms or adverse reaction were assumed to switch to

erythromycin. Amoxicillin was the assumed treatment for patients presenting with otitis media or sinusitis as complication.

The cost of GP consultation was taken from 'Unit costs of health and social care', Personal Social Services Research Unit (PSSRU), 2010 (35). The duration of consultation was assumed to be lower than the average consultation (35); following the expert opinion of the NICE Guideline Development Group (GDG) who estimated consultation for sore throat would only take 8 minutes (12).

The UK National Schedule of Reference Costs 2010-11 for NHS Trusts (34) was used to identify cost and resource use data for the management of adverse reaction to antibiotics of anaphylaxis and the complication of quinsy. Diagnostic codes for anaphylaxis and quinsy were mapped onto health resource use data, where the cost and duration of stay were ascertained. Cost of overall complications was calculated as a weighted average of the number of people expected to experience otitis media, sinusitis or quinsy.

The costs of the interventions were calculated individually. In the base case, for written information, the duration of consultation remained constant as adherence information was assumed to be integral to a consultation for sore throat that involved the prescribing of antibiotics. The cost of producing written information included set-up and printing costs (38). It was assumed that the information sheet would be available online for GPs to print locally during the consultation.

In the base case analysis of telephone back-up, the duration of telephone reminder was assumed, from clinical opinion, to be 5 minutes. The cost of GP telephone consultation reported by the UK PSSRU (2010) (35) was assumed to be equivalent of telephone back-up. No additional costs were considered for the telephone back-up intervention. In both cases the interventions were assumed to be provided by the GP in the base case.

7.16 Sensitivity analysis

Sensitivity analyses on the duration of consultation associated with the provision of information adherence-enhancing interventions were conducted. First we considered a one minute increase in consultation – to administer the written information; secondly, a one-minute reduction in telephone back-up consultation.

Table 7.6: Summary of utility weights, and ranges for the sensitivity analyses

Health state: Utility weights	Base	Lower	Upper	Source / comments
No sore throat	0.86	0.72	1	UK population norm for EQ-5D (Kind et al. 1999) (32).
Sore throat	0.81	0.67	0.95	Based on the disutility of pharyngitis taken from Neuner et al. (2003) (30).
Adverse events to antibiotics (anaphylaxis)	0.36	0.22	0.5	Based on the disutility of the assumption used in NICE (2008) (12).
Complications	0.36	0.22	0.5	Based on the disutility of the assumption used in NICE (2008) (12).
Duration				
Sore throat	5 days	3 days	7 days	Base case: Little et al. (1997) (27) (average number of days with symptoms). Upper: average total illness length of acute sore (NICE 2008) (12).
Adverse events to antibiotics (anaphylaxis)	1 day	1 day	2 days	National schedule of reference costs 2009-10 (34): Number of days taken from estimated length of stay for anaphylactic shock (HRG code CZ22Y).
Complications	1 day	1 day	2 days	National schedule of reference costs 2009-10 (34): Number of days taken from estimated length of stay for quinsy (HRG code WA16Y).

Table 7.7: Summary of unit cost estimates, and ranges for the sensitivity analyses: control/intervention

Costs	Base	Lower	Upper	Source / comments
Antibiotics (per course)				
Penicillin V 500mg TDS 10 days	£3.57		£6.60	Drugs Tariff, September 2011(33). Upper includes £3.03 prescribing charges for dispensing cost of community pharmacy UK (PWC 2011) (37).
Erythromycin 250mg QDS 10 days	£2.53		£5.56	Drugs Tariff, September 2011 (33). Upper includes £3.03 prescribing charges for dispensing cost of community pharmacy UK (PWC 2011) (37).
Amoxicillin 500mg TDS 5 days	£1.41		£4.44	Updated: Drugs Tariff, September 2011 (33). Upper includes £3.03 prescribing charges for dispensing cost of community pharmacy UK (PWC 2011) (37)
Secondary care and outpatient costs				
GP consultation, £3.10 per min	£24.80	-	£36.27	PSSRU 2010 (35) using original assumption of an 8-minute consultation (GDG consensus) including direct care staff costs and with qualification costs. Upper uses a 11.7 min surgery consultation as reported in PSSRU 2010 (35)
Hospitalisation cost for peritonsillar abscess (quinsy) for adults	£447.00	£304.00	£530.00	National schedule of reference costs 2009-10 (34) using HRG code WA16Y - Shock and Anaphylaxis without CC. Non-elective. Average length of stay reported as 1 day (34).
Hospitalisation cost for anaphylaxis for adults	£350.00	£229.00	£423.00	National schedule of reference costs 2009-10 (34) using HRG code CZ22Y - Intermediate head, neck and ear disorders 19 years and over without CC. Non-elective. Average length of stay reported as 1 day (34).
Cost of complications				
Cost of complications with antibiotics	£133.57			Calculated using cost data outlined above and probabilities in tables 7.4 and 7.8.
Cost of complications with no antibiotics	£218.65			Calculated using cost data outlined above and probabilities in tables 7.4 and 7.8.

Table 7.8: Probabilities used to calculate the costs of complications, and ranges for the sensitivity analyses

Probabilities	Base	Lower	Upper	Source / comments
Develop otitis media with antibiotics	0.00585	-	-	Del Mar et al. (2006)(28)
Develop sinusitis with antibiotics	0.002304	-	-	Del Mar et al. (2006) (28)
Develop quinsy with antibiotics	0.003465	-	-	Calculated from data in the NICE report (12).
Develop otitis media with no antibiotics	0.0195	-	-	Del Mar et al. (2006) (28). Calculated by taking the number of patients experiencing otitis media with no antibiotics over the total number of patients in the control arms.
Develop sinusitis with no antibiotics	0.0048	-	-	Del Mar et al. (2006) (28). Calculated by taking the number of patients experiencing sinusitis with no antibiotics over the total number of patients in the control arms
Develop quinsy with no antibiotics	0.0231	0.002	0.2	Del Mar et al. (2006) (28). Calculated by taking the number of patients experiencing quinsy with no antibiotics over the total number of patients in the control arms

Table 7.9: Summary of unit cost estimates, and ranges for the sensitivity analyses: adherence-enhancing intervention

Intervention costs	Base	Lower	Upper	Source / comments
Administration of written information intervention, £3.10 per minute	0	-	£3.10	PSSRU 2010 (35) unit costs / minute consultation including direct care staff costs and with qualification costs. Base case: assumed intervention integral to routine consultation. Upper: Additional minute for administration of written information.
Written information leaflet	£0.03	£0.02	£0.04	Cost of paper and printing estimated at £0.015 per leaflet. Set-up costs calculated using Link et al. (2006) (38) assuming 495 cases per GP practice per year and one version per PCT / SHA in England and Wales.
Administering the telephone back-up intervention, £3.09 per minute	£15.49	£12.40	22.00	PSSRU 2010 (35) unit cost / minute telephone consultation including direct care staff costs with qualifications. Duration assumed to be 5 minutes based on clinical opinion in UK. Upper: Mean duration of telephone consultation of 7.1 minutes as reported in PSSRU (2010) (35). Lower: reduction of one minute.

7.17 Results

7.17.1 Base case

In the base case analysis, the expected cost of immediate antibiotic prescribing was £40.48 (table 7.10). This reduced to £40.12 when written information was provided to improve adherence. The total cost per patient of delayed prescribing was £15.23 (table 7.11). The lowest cost delayed prescribing strategy inclusive of an adherence-enhancing intervention was £16.35, with telephone back-up.

The model estimated very small differences in QALYs between strategies; such small differences can be attributed to the short-time frame and relatively mild severity of sore throat (NICE 2009) (12). The results of the QALY analysis are shown in table 7.10 and table 7.11. The strategy of immediate antibiotics prescription with written information was less costly and more effective than immediate prescription only – it is therefore dominant and the most preferable strategy when immediate prescribing is necessary. The model of the delayed prescription strategy with written information indicated that it was associated with an incremental cost-effectiveness ratio (ICER) of £8,719 per QALY gained, versus delayed antibiotics (without an adherence-enhancing intervention).

7.17.2 Sensitivity analysis on costs of adherence-enhancing intervention

A one-way sensitivity analysis, conducted to vary the costs of providing adherence-enhancing interventions demonstrated that the ICER was highly sensitive to the duration of consultation. In the case of immediate prescribing with written information, an increase of one minute resulted in an ICER of £11,842 per QALY gained, versus immediate prescription only; this strategy was previously dominant (table 7.12). A decrease in the duration of the telephone call from 5 minutes to 4 minutes resulted in a more favourable ICER for immediate prescribing with telephone back-up versus immediate prescription with written information, but the telephone back-up intervention remained dominated by the written information intervention (table 7.12).

In the case of delayed prescribing with written information, an increase of one minute resulted in an increase of the ICER from £8,719 per QALY gained, to £9,062 per QALY gained, versus delayed prescription only (table 7.13). A decrease in the duration of the telephone call from 5 minutes to 4 minutes, resulted in a decrease in the ICER for delayed prescribing with telephone back-up versus immediate prescription with written information (£16,230 to £14,728 per QALY gained), but this remained dominated by the written information strategy (table 7.13).

Table 7.10: QALY model for immediate prescription

IMMEDIATE BASE CASE	Cost per person	QALYs per person	ICER	Versus
Immediate antibiotics + written information	£40.12	0.8580	Dominant	-
Immediate antibiotics only	£40.48	0.8577	Dominated	Immediate antibiotics + written information
Immediate antibiotics + telephone back-up	£56.72	0.8578	Dominated	Immediate antibiotics + written information

Table 7.11: QALY model for delayed prescription

DELAYED BASE CASE	Cost per person	QALYs per person	ICER	Versus
Delayed antibiotics only	£15.23	0.8465	-	
Delayed antibiotics + telephone back-up	£16.35	0.8465	Dominated by extended dominance (£16,230 per QALY gained)	Delayed antibiotics only
Delayed antibiotics + written information	£17.57	0.8467	£8,719.41	Delayed antibiotics only

Table 7.12: Sensitivity analysis on duration of consultation for adherence-enhancing intervention for immediate prescription: all other parameters at base case values

SENSITIVITY ANALYSIS: GP CONSULTATION DURATION	Cost per person	QALYs per person	ICER	Versus
Immediate antibiotics only	£40.48	0.8577	-	
Immediate antibiotics + written information + additional min of consulting time	£43.37	0.8580	£11,841.89	Immediate antibiotics only
Immediate antibiotics + telephone back-up	£56.72	0.8578	Dominated	Immediate antibiotics + written information + additional min of consulting time
SENSITIVITY ANALYSIS: TELEPHONE BACK-UP DURATION	**Cost per person**	**QALYs per person**	**ICER**	**Versus**
Immediate antibiotics + written information	£40.12	0.8580	Dominant	
Immediate antibiotics only	£40.48	0.8577	Dominated	Immediate antibiotics + written information
Immediate antibiotics + telephone back-up - minute reduction of telephone call	£53.45	0.8578	Dominated	Immediate antibiotics + written information

Table 7.13: Sensitivity analysis on duration of consultation for adherence-enhancing intervention for delayed prescription: all other parameters at base case values

SENSITIVITY ANALYSIS: CONSULTATION DURATION	Cost per person	QALYs per person	ICER	Versus
Delayed antibiotics only	£15.23	0.8465		
Delayed antibiotics + telephone back-up	£16.35	0.8465	Dominated by extended dominance (£16,230 per QALY gained)	Delayed antibiotics only
Delayed antibiotics + written information + additional min of consulting time	£17.66	0.8467	£9,061.83	Delayed antibiotics only
SENSITIVITY ANALYSIS: TELEPHONE BACK-UP DURATION	**Cost per person**	**QALYs per person**	**ICER**	**Versus**
Delayed antibiotics only	£15.23	0.8465		
Delayed antibiotics + telephone back-up - minute reduction of telephone call	£16.25	0.8465	Dominated by extended dominance (£14,728 per QALY gained)	Delayed antibiotics only
Delayed antibiotics + written information	£17.57	0.8467	£8,719.41	Delayed antibiotics only

7.18 Discussion

The review of the cost-effectiveness literature over the past 30 years shows a distinct lack of evidence on the cost-effectiveness of adherence-enhancing interventions. Very few studies were identified that were full economic evaluations, which probably reflects an *ad hoc* approach to adherence research, an assumption that any improvement in adherence is likely to be cost saving, and a perception that economic evaluations are of marginal importance in many prominent areas of the literature, such as in relation to treatments for HIV, tuberculosis and organ transplantation. However, this does not detract from the increasingly central role of health economics in informing decisions on the allocation of healthcare resources, and the need for quality evidence on cost-effectiveness. More research is required on the robust assessment of clinically effective interventions to improve medication adherence.

Our review of the clinical effectiveness of interventions to improve adherence to antibiotics for the management of upper respiratory tract infection identified two approaches which focus on education (verbal and written information) (25) and a combination of education and behavioural counselling (verbal and telephone back-up) (24). The interventions were shown to improve adherence by 25% and 53%, respectively, but had no significant impact on clinical cure rates (RR 0.96 95%CI 0.84 to 1.01) (25) and (RR 1.11 95%CI 0.87 to 1.42) (24). The evidence was from two pragmatic trials, we therefore refer to effectiveness rather than efficacy throughout. One difficulty in the interpretation of the results on health outcomes relates to the correlation between subjective improvement cure rates and non-adherence, as improvement in symptoms was the primary reasons for treatment discontinuation. Oversight was also a common reason given for early discontinuation. Together, these represent intentional and non-intentional non-adherence, respectively. Reasons for non-adherence may be explained by multiple theoretical models that explain behaviour and may therefore be beneficial in the development of adherence-enhancing interventions (39). The educational interventions tend to address the benefits of adherence more than overcoming barriers. Besides an assumption of an adequate level of literacy, interventions based on written information alone are unlikely to effect a significant and lasting behaviour change; as remote interventions generally yield a lower relative improvement in adherence (40). Further benefit may be derived from information addressing psychological barriers to adherence and other factors that have been found to be significant predictors of medicines adherence (39).

The economic evaluation suggests that a strategy of written information to enhance adherence to antibiotic for acute sore throat is cost-effective for both delayed and immediate prescribing strategies. The analysis benefits from modelling interventions which are practicable for implementation in routine practice, and which can be adopted alongside prescribing strategies that are currently recommended for use in primary care (12). Websites that are recommended to patients, for example www.patient.co.uk (41), could potentially host the information. This website, as one example, currently offers information on acute sore throat (e.g. tonsillitis) and antibiotics (e.g. phenoxymethylpenicillin), that may be used / and or referred to in routine practice. The UK NHS

Institute for Innovation and Improvement actively encourages provision of good patient information, often in written form (42). Similarly, telephone consultations are used in routine clinical practice and procedures could be modified / enhanced to include the provision of telephone back-up strategies. Whilst the base case analysis assumes the prescribing general practitioner would provide the intervention, in line with the source data (24, 25), this may be provided by other healthcare professionals, such as a nurse or pharmacist. Although this scenario could be modelled, we resisted from doing so on the basis that it would require an assumption, without supporting evidence, that different professionals would achieve the same impact on adherence at a lower cost. Healthcare professionals' roles may vary across Europe and this would need to be considered on a country by country basis.

7.19 Limitations

There are some caveats to the economic analysis, which require careful consideration when interpreting the results, in particular as the sensitivity of the incremental cost-effectiveness ratios to small changes in parameter estimates. The economic evaluation did not consider the effects of the intervention over time. The use of adherence-enhancing interventions over multiple courses of acute treatment may be expected to diminish overtime, as the patient becomes more familiar with the additional information or familiar with the telephone call. Conversely the patient may retain more information over time, or anticipate the telephone call, with positive effect. Evidence suggests that interventions involving repeated feedback are amongst the most common and effective forms of adherence-enhancing intervention for chronic conditions (43, 44), but there is limited evidence on repetition of adherence-enhancing interventions in individual episodes of acute treatment. Similarly, the adherence-enhancing interventions described here may not be practical in the long term – where patients are given repeat prescriptions with less frequent review.

The influence of adherence-enhancing interventions on consultation duration and the potential requirement of training healthcare professionals to deliver the intervention warrants further investigation, as it is likely that consultation duration may increase with the provision of additional information. Although it is anticipated that adherence to antibiotic prescription is routinely discussed – the written information would be intended to reinforce this beyond the consulting room. Telephone back-up is unlikely to increase the initial consultation duration, however, the provision of a back-up telephone call, may be viewed as an additional consultation. The remit of this telephone intervention and the capacity to deal with further clinical queries, need to be defined; patients' preferences for telephone back-up could also be investigated, as the back-up may be viewed as additional care.

Finally, the analysis did not consider the evolution and spread of antibiotic resistance, did not measure patient preferences (health state utilities) directly, and as with most economic evaluations, was based on a secondary analysis of disparate sources of evidence (45). This required assumptions concerning the generalisability of the results across studies, and to current UK primary care setting. Whilst more robust evidence on the costs and effectiveness of these interventions

would be desirable, it is highly unlikely that a trial comparing the treatment strategies would be conducted.

7.20 Implications and recommendations

The addition of written information, during GP consultations, to: (i) emphasise the importance of completing the antibiotic treatment, (ii) respect intervals between doses and (iii) detail the drawbacks of an early dropout, is a cost-effective approach to immediate or delayed antibiotic prescribing in URTI, as per the UK NICE (2008) clinical guidelines (12). The economic evaluation suggests that interventions targeted at acute conditions with small health benefit will need to have a low per patient cost to be economically worthwhile. A degree of caution is required in interpreting the results, however, as they are sensitive to small changes in parameter estimates.

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8 Preparation of policy recommendations for supporting medication adherence in European healthcare.

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We are also grateful to six anonymous medicines policy experts from Denmark, Finland, Germany, Ireland, Latvia and Lithuania for their participation in this study.

European Forum on Patient Adherence to Medication

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8.1 Summary

This chapter takes a broad policy and implementation focus. A number of initiatives, events and studies are described which together aim to provide evidence-informed solutions to optimise medicines use to achieve clinical and cost-effective use of medicines across Europe. First a new educational framework for European healthcare professionals is presented. The development of the framework is described and ways in which the framework can be used by educators, healthcare providers and healthcare professionals is documented. The educational framework has been circulated to all School of Medicines, Nursing and Pharmacy in Europe to promote consistency and shared learning in medical education about medication adherence. Next, we describe a Delphi study and consensus meeting which were used to reach consensus amongst a broad range of adherence stakeholders about policy solutions to address medication adherence for Europe. We then describe a key informant study which invited national medicines policy leads for EU member states to self-assess the level of implementation of medicines adherence initiatives in their country, and the adequacy of that implementation. Interviews with the medicines leads enabled in-depth understanding of the variation in adherence support across nations, and the ways in which difference nations prioritise, plan and implement medicines adherence systems and services. Finally, we bring together the research-based recommendations for medication adherence from earlier chapters, which were presented and discussed at a ABC Project dissemination event in December 2011 at the European Parliament Building.

8.2 Introduction

At any one time, a substantial minority of the European population prescribed medication for the prevention or treatment of illness are non-adherent to that medication. The consequences of non-adherence, which can include avoidable morbidity and mortality, waste of health resources and sub-optimal care, point to the need for a health policy response to medication non-adherence. The overarching objective of the ABC project is to produce policy recommendations to aid clinical and cost-effective use of medicines in Europe.

The nature of the relationship between research and healthcare policy has been conceptualised in a number of ways. Traditional models propose a straightforward linear, rational process in which research knowledge is transferred to policy makers. Contextual and multidimensional models instead propose that the reductionist approach of linear models simplifies the nature of the relationship between research and policy, and fail to take account of the broader range of influences on policymakers, the range of stakeholders involved in the policy influencing process, and the competing priorities that policymakers juggle.[1 2 3]

It has been noted that ‘research on the effectiveness of policies will never be more than one of the factors that must be considered by policymakers’ (Ettelt & Mays[4], p. 171). In this chapter, we seek to aid medicines policymakers in policy formulation, by developing a set of policy solutions prioritised

according to their importance, operational and political feasibility. In so doing we aim to move beyond the research evidence and towards the policy arena.

The medication adherence field is characterised by a number and variety of stakeholders, including patients and the public, healthcare professionals, academics, healthcare service providers, industry and policymakers. Some initiatives have made concerted efforts to bring people together from variety of stakeholders to agree on priorities, particularly in the USA (such as the medication adherence campaign coordinated by the USA National Consumers League, http://scriptyourfuture.org/). This chapter describes the first attempts we know of to do this at European level. We present a Delphi study to reach consensus amongst a group of adherence stakeholders about policy options to address medication non-adherence. Further, we describe two European meetings to develop and disseminate research evidence and policy recommendations for medication adherence with multi-stakeholder participation.

Whilst a number of initiatives have proposed cues to action and clinical guidelines to inform clinical practice, as we saw in Chapter 5, there have been rather more limited attempts to develop policy recommendations for policymakers at European and national level, or to explore the views of policymakers that have a brief that includes medication adherence. Little is known about how policymakers perceive the state of the art in medication adherence interventions or the extent and adequacy of policy implementation to support medication adherence. Here, we present a key informant study in which policymakers self-assess policy implementation in their own country and discuss the range of influences on their policy decision making. We also take the opportunity to ask policymakers to reflect on the policy options presented in this chapter.

We draw this report to a close by bringing together the consensus-based recommendations developed in this chapter with the research-based recommendations described in earlier chapters. Finally we consider the next steps that are necessary to support effective policy implementation to support medication adherence in Europe in the future.

8.3 Objectives

- To develop a common European educational framework specifying curriculum for schools of medicine, pharmacy and nursing for managing and supporting patients with medication adherence
- To reach consensus among medication adherence stakeholders on strategies to address patient adherence
- To develop policy recommendations for enhancing medication adherence in Europe
- To tailor medication adherence policy recommendations toward the needs of different healthcare settings and population segments, taking into account cultural differences between European regions.

8.4 Managing and supporting medication adherence: a framework for the education and training of health professionals in Europe

8.4.1 Introduction

With more patients taking medicines than ever before, encouraging patients to get the most out of their medicines is essential to avoid unnecessary ill health as well as reduce waste and unnecessary cost. Since the decision about whether to take a medicine or not ultimately lies with the patient it is crucial that health professionals and patients engage in a partnership approach to consultations to manage and support adherence to medicines. This needs to be underpinned by appropriate education and development for health professionals. This section sets out an educational framework for appropriate education and development of health professionals in Europe on managing and supporting medicines adherence with patients.

The educational framework presented is principally aimed at the professions of medicine, pharmacy and nursing in Europe, but also applies to any health professional engaging in discussions with patients about their medication. The framework comprises four parts: a competency framework describing the skills, knowledge, attributes and behaviours of healthcare professionals that can support patients with medicines; a curriculum for educational organisations to guide education and training for healthcare professionals in their work with patients and their medicines; and a diagnostic tool that can be used both by healthcare professionals to reflect on their practice against specific criteria and by educational organisations to assess their curricula against the competencies that healthcare professionals need to support patients with medicines and medicines taking. The educational framework ends with a brief reading list for managing and supporting medication adherence.

8.4.2 Method

The starting point for the production of the framework was a competency framework for shared decision-making with patients for taking medicines, produced in 2007.[5] The document also details the robust methodology used to develop the competency framework. As part of the ABC project, this competency framework was developed and updated by a review of the literature, a formal process of consultation and review by the ABC project reference group to form a new educational framework for health professionals in Europe on managing and supporting medication adherence.

The literature search was undertaken to identify new evidence published since the development of the 2007 competency framework. Literature searches of EMBASE, MEDLINE and the Cochrane Database were undertaken to identify relevant publications in the English language using combinations of the following key words: patient compliance, medication adherence, communication skills, health professional, curriculum, medical education, nursing education, pharmacy education

and professional development. Boolean operators and MeSH terms were used wherever possible. Relevant publications included competency frameworks, curricula, guidance, standards or consensus statements on medicines adherence, or the education and training of health professionals on medicines adherence or aspects of managing and supporting medication adherence. Systematic reviews and other high-quality evidence related to managing or supporting medicines adherence were also included. In addition, the grey literature (i.e. documents that have not been published in peer-reviewed journals) was searched using the same key words in online search engines such as Google for competency frameworks, curricula, guidance, standards or consensus statements on medicines adherence, or the education and training of health professionals on medicines adherence or aspects of managing and supporting medication adherence. Documents not in the English language were scrutinized for relevance by using the translation function of search engines.

In order to ensure that the competency framework is relevant to all current and future health professionals engaging with patients across Europe, a wide range of over 250 individuals and organisations in Europe were invited through a formal consultation process to comment on how the competency framework should be updated. These individuals and organisations included: national and European patient groups; national and European organisations representing doctors, nurses, and pharmacists; a random sample of 5 schools of medicine, 5 schools of nursing and 5 schools of pharmacy from each EU member country and all European organisations representing schools of medicine, nursing and pharmacy. These individuals and organisations were sent an email on the 8th September 2011 inviting them to share their ideas on how we can update the competency framework for shared decision-making with patients. Attached to this email were the consultation document, which described the purpose of the proposed competency framework and a link to the existing competency framework, and the questionnaire to use to share their ideas. On the 3rd of October 2011, reminders were sent by email to all organisations invited to participate in the consultation, with final reminders sent a week later. The consultation closed on the 17th of October 2011. Individual statements were identified in responses to the consultation and carefully considered by the educational framework development team. From these statements, the curriculum development team updated and adapted the framework. The team also mapped the competency framework to the common curriculum for managing and supporting medication adherence and the diagnostic tool for assessing competence in managing and supporting medication adherence.

The first draft of the complete educational framework document was reviewed by the ABC project reference group and circulated to the ABC project partners for comment, with the intention that comments received could be used to confirm the content of the final document. It was then desktop published in coverflow portable document and iBook formats to increase accessibility. The coverflow version was circulated to all the ABC partners for comment. Comments received were used to confirm the content and presentation of the final document.

8.4.3 Results

The literature search of MEDLINE, EMBASE and the Cochrane library returned no competency frameworks, curricula, guidance, standards or consensus statements specifically concerned with the education and training of health professionals on medication adherence. Consensus statements were however found for communication with patients, a crucial aspect of managing and supporting medication adherence.[6] [7] These statements were found to be broadly consistent with the competency framework that the educational framework development started with. Several studies were found that identified and described current policy, education and research concerned with medication adherence in a number of countries, including European countries such as Denmark,[8] England,[9] Finland,[10] Spain,[11] Sweden, and Switzerland.[12] Each study reviewed published research articles from that country indexed in major databases, current policy documents available from the websites of relevant governmental and professional organisations in that country, and most conducted questionnaire surveys of schools of pharmacy in that country on the adherence-related courses provided. These studies are valuable in that they provide brief details about learning activities related to adherence provided in undergraduate and postgraduate courses in many of the schools of pharmacy in these countries, which is useful for comparison,[13] but they do not outline learning outcomes or competencies related to adherence in these courses that could inform the development of the educational framework. In addition, a number of systematic reviews related to medication adherence were found, such as Joosten and colleagues'[14] review on shared decision-making and van Dulmen and colleagues' review of 38 systematic reviews of adherence interventions.[15] These informed the development of the educational framework by identifying issues that could be included in the content of educational programmes about adherence, rather than competencies or learning outcomes associated with that content.

The search of the grey literature returned various types of document at European and national level related to the education and training of health professionals, but adherence appeared to be embedded within other topics in these documents and no single document contained a section on managing or supporting patients' adherence to prescribed medication. Furthermore, the necessity for broad learning outcomes or objectives often mitigates against the inclusion of very specific topics, such as medication adherence. At a European level these documents included EC directives such as 2005/36/EC, which includes arrangements for reciprocal recognition of health professional qualifications across Europe, and EC funded project reports and associated documents concerned with the professions of medicine and pharmacy (e.g. MEDINE and PHARMINE). At a national level these included current policy documents, documents (e.g. guidance and consultations about updating it) from nationally funded organisations such as the UK National Institute of Health and Clinical Excellence (NICE),[16] [17] and standards and guidance produced by health professional regulatory or professional bodies responsible for the education and training of particular health professions. UK examples of these include *Tomorrow's Doctors*,[18] *Future Pharmacists*,[19] and *Standards for pre-registration nursing education*.[20] To illustrate the above point on adherence being embedded in broad learning outcomes, standards or competencies in these documents relevant to

managing medication adherence are included as appendix 8.1. In addition, a number of reports were found that had been produced by independent authors or organisations, including for example *Just What the Doctor Ordered*,[21] which provided a 'core curriculum for patient adherence'. This mapped perceived professional practice gaps with educational objectives, strategies and content and although orientated towards practice in the US, was nevertheless helpful in informing the content of the common curriculum in the educational framework. Other examples, such as the LLAKES report on modernizing the pharmacy curriculum[22] did not refer to medication adherence, whilst the Cribb report on shared decision-making and medicines[23] and the RAND report[24] were positioned at a policy level rather than being specifically concerned with education and training of health professionals.

Seven responses to the consultation were received. However, several of these were detailed and insightful. This directly resulted in substantial and fundamental changes being made to the competency framework used as the starting point for the development of the educational framework. The full content of the responses received is shown in Appendix 8.2 together with detailed statements as to how each point made in each response was considered in relation to developing the educational framework.

The resulting educational framework comprises four parts: a competency framework describing the skills, knowledge, attributes and behaviours of health professionals in supporting patients with medicines (Figures 8.1 and 8.2); a curriculum for educational organisations to guide education and training (Figure 8.3); and a diagnostic tool for health professionals to reflect on their practice and against which educational organisations can assess their curricula (Figure 8.4). The framework includes a reading list. The educational framework can also be viewed here: http://abcproject.eu/img/ABC%20Project%20Medicines%20Adherence%20Educational%20Framework.pdf

8.4.4 Discussion

This educational framework for managing and supporting medication adherence was principally developed for the professions of medicine, pharmacy and nursing, although it will also be of relevance to other health professions that are involved in medicines adherence. The framework of competencies and the diagnostic tool for assessing competence included in the educational framework should help individuals and teams to effectively manage and support medication adherence with patients. They are best used as a starting point for discussion of competencies required by individuals or teams. Specifically, they can be used by education and training providers in the initial education of health professionals and in competency-led postgraduate training

Figure 8.1. A competency framework for managing and supporting medication adherence with patients - Overview

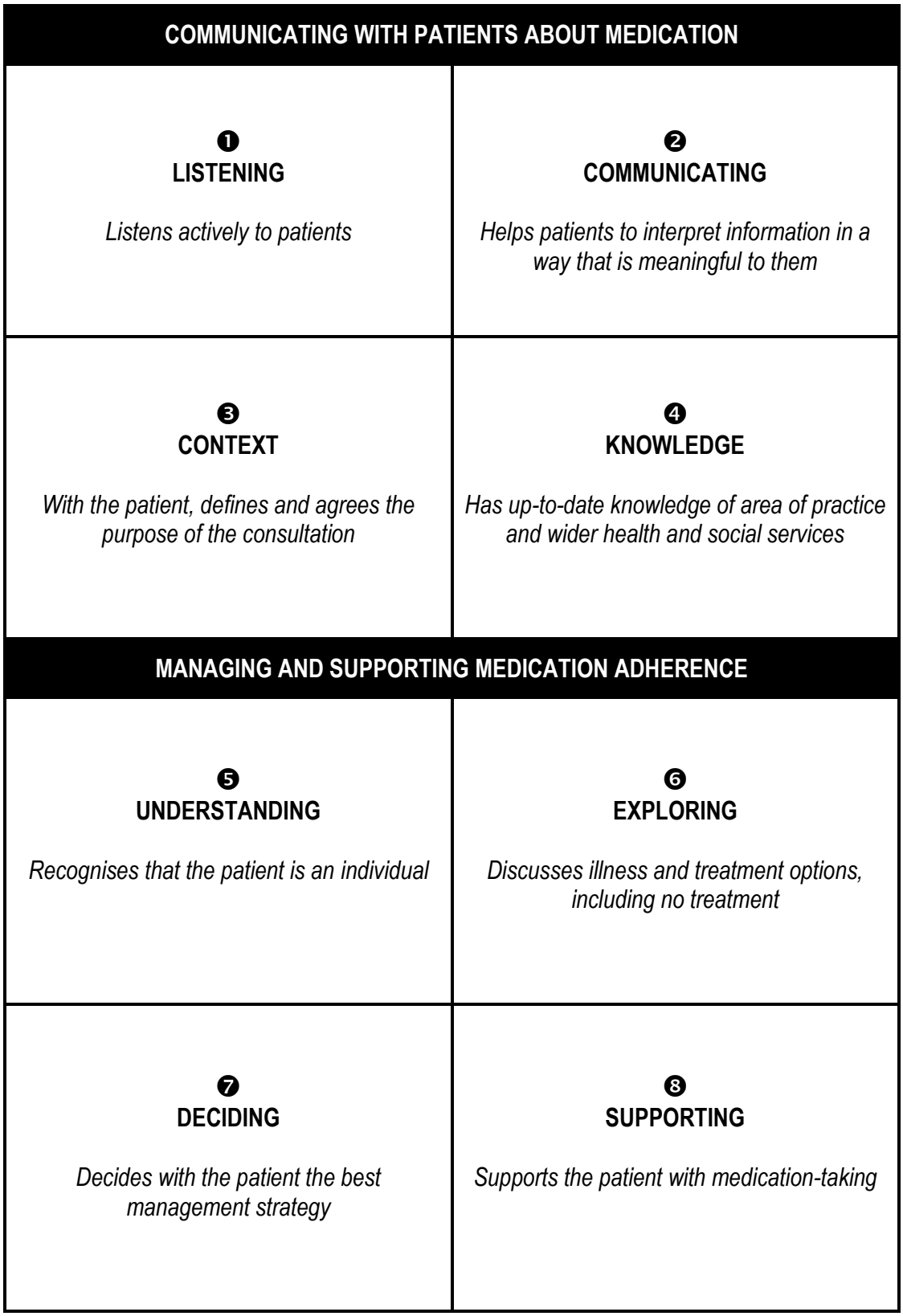


Figure 8.2. The competency framework for managing and supporting medication adherence with patients

COMMUNICATING WITH PATIENTS ABOUT MEDICATION	
1. LISTENING ***Listens actively to the patient***	**2. COMMUNICATING** ***Helps patients to interpret information in a way that is meaningful to them***
1. Helps patients feel at ease and feel that you have time for them 2. Gives the patient the opportunity to express their views 3. Listens to the patient's views and discusses any concerns 4. Encourages the patient to ask questions about their condition 5. Allows time for questions 6. Treats the patient as an equal partner 7. Respects diversity 8. Expresses willingness to be flexible	1. Identifies barriers to communication and responds appropriately 2. Shares knowledge and information in a way that the patient understands 3. Explores and confirms the patient's understanding 4. Checks own understanding of the patient's viewpoint 5. Uses aids to help understanding (e.g. decision aids and question prompts) 6. Recognises the importance of non verbal communication and responds appropriately 7. Uses questions to elicit information 8. Maintains appropriate eye contact 9. Displays a non judgemental attitude
3. CONTEXT ***With the patient, defines and agrees the purpose of the consultation***	**4. KNOWLEDGE** ***Has up-to-date knowledge of area of practice and wider health and social services***
1. Reviews patient information prior to the consultation 2. Introduces and explains own role 3. Establishes how involved the patient wants to be in decisions about their treatment 4. Clarifies the timing, boundaries and expectations of the consultation 5. Ensures that the consultation takes place in an appropriate setting and minimises interruptions 6. Keeps focused on the agreed aims of the consultation	1. Knows own limitations 2. Maintains up-to-date professional knowledge and skills appropriate to own role 3. Knows when and how to seek further advice 4. Refers on to other health professionals and social services as required or as requested 5. Works in partnership with colleagues 6. Shares up-to-date information with patients about specialist support and community resources 7. Is aware of practical resources to help patients
▪ Managing and supporting medication adherence with patients may also involve others, e.g. family members, carers and advocates ▪ Health professionals clearly need a wide and variable range of competencies in their consultations with patients. This framework concentrates on the competencies that any health professional might need when engaging with patients in managing and supporting medication adherence and should be used in conjunction with other professional and organisational frameworks	

MANAGING AND SUPPORTING MEDICATION ADHERENCE	
5. UNDERSTANDING ***Recognises that the patient is an individual***	**6. EXPLORING** ***Discusses illness and treatment options, including no treatment***
1. Seeks to understand the patient's current circumstances and previous experiences (including, for example, age, gender, disability, mental health, lifestyle, health literacy and socioeconomic status) that may impact on treatment 2. Is aware of whether the patient's cultural, religious or societal beliefs impact on treatment 3. Explores what the patient thinks about medicines in general 4. Respects the patient's expertise and knowledge of their condition	1. Explores what the patient has been doing to deal with symptoms / illness and what the patient understands about their treatment 2. Discusses with the patient their expectations and concerns about their illness and treatment 3. Provides full, accurate and understandable information about the patient's symptoms / illness and the benefits, effects, risks (e.g. side effects) and uncertainty of all treatment options 4. Discusses prognosis and likely health outcomes 5. Establishes whether the health professional and the patient have similar or different views about the patient's symptoms / illness 6. Discusses any misunderstandings about illness or treatments 7. Encourages the patient to express positive and negative views about treatment and no treatment options
7. DECIDING ***Decides with the patient the best management strategy***	**8. SUPPORTING** ***Supports the patient with medication taking***
1. Discusses the patient's preferred option for treatment, negotiates treatment goals and decisions, but accepts the patient's final decision 2. Gives the patient time to consider the information before making a decision, if appropriate 3. Maintains appropriate professional records about decisions that are made and their outcomes 4. Explores the patient's ability to undertake the agreed plan 5. Checks that the patient knows what medicines they are taking and why 6. Discusses when treatment will be reviewed (and what this entails), changed or stopped 7. Ensures that the patient knows what to do if their symptoms change, do not improve, or if a problem arises (e.g. a side effect)	1. Recognises non-adherence (identifies patients at risk of non-adherence, assesses patients' adherence, for example by asking if they have missed any doses of their medication, and recognises the effects of non-adherence) 2. Identifies reasons for / causes of non-adherence, and barriers to future adherence 3. Manages adherence by providing effective practical support where the patient needs / wants help with adherence 4. Supports patients by providing ongoing information and feedback (including encouraging patients to come back with any questions), and monitors adherence
▪ Managing and supporting medication adherence with patients may also involve others, e.g. family members, carers and advocates ▪ Health professionals clearly need a wide and variable range of competencies in their consultations with patients. This framework concentrates on the competencies that any health professional might need when engaging with patients in managing and supporting medicines adherence and should be used in conjunction with other professional and organisational frameworks	

Figure 8.3. A common curriculum for managing and supporting medication adherence with patients

COMPETENCY AREA	LEARNING OUTCOMES	EDUCATIONAL CONTENT
Communicating with patients about medication	1. Listen actively to patients 2. Help patients to interpret information in a way that is meaningful to them	Theory, evidence, best practice and techniques on: • Effective patient centred communication, including non-verbal communication, in relation to medications • Reflecting on and developing communication skills
	3. Define and agree the purpose of consultations with patients 4. Demonstrate up-to-date knowledge of area of practice and wider health and social services	Theory, evidence, best practice and techniques on: • How to effectively prepare for and manage consultations with patients • Maintaining up-to-date professional knowledge and skills appropriate to own role • Maintaining up-to-date knowledge of effective interventions and practical resources to support patients with medication adherence, and current terminology on adherence • Evaluating and improving / developing broad strategies and policy aimed at managing and supporting adherence • Working in partnership with colleagues and service providers to support patients with medication adherence
Managing and supporting medication adherence	5. Recognise that the patient is an individual 6. Discuss illness and treatment options, including no treatment 7. Decide with the patient the best management strategy 8. Support the patient with medicine-taking	Theory, evidence, best practice and techniques on how to: • Understand the patient's current circumstances and previous experiences and how these may impact on their beliefs and behaviour about their illness and its treatment. This includes recognising beliefs and behaviours found to be detrimental to adherence (e.g. low self-efficacy) • Discuss with the patient their current symptom experience and management, and health outcomes related to treatment options, including no treatment. • Discuss and agree with the patient their preferred option for treatment and the treatment decision • Recognise non-adherence (i.e. identify patients at risk of non-adherence, assess patients' adherence and recognise the effects of non-adherence) • Identify reasons for / causes of non-adherence, and barriers to future adherence • Manage adherence by providing effective practical support where the patient needs / wants help with adherence • Support patients by providing ongoing information and feedback (including encouraging patients to come back with any questions), and monitoring adherence

Figure 8.4. A diagnostic tool for assessing competence in managing and supporting medication adherence

COMMUNICATING WITH PATIENTS ABOUT MEDICATION					
	ATTRIBUTE	**RATING** (tick ONE box only for each attribute)			
		ALWAYS	**USUALLY**	**SOMETIMES**	**NEVER**
1. LISTENING	Helps patients feel at ease and feel that you have time for them				
	Gives the patient the opportunity to express their views				
	Listens to the patient's views and discusses any concerns				
	Encourages the patient to ask questions about their condition				
	Allows time for questions				
	Treats the patient as an equal partner				
	Respects diversity				
	Expresses willingness to be flexible				
2. COMMUNICATING	Identifies barriers to communication and responds appropriately				
	Shares knowledge and information in a way that the patient understands				
	Explores and confirms the patient's understanding				
	Checks own understanding of the patient's viewpoint				
	Uses aids to help understanding (e.g. decision aids and question prompts)				
	Recognises the importance of non verbal communication and responds appropriately				
	Uses questions to elicit information				
	Maintains appropriate eye contact				
	Displays a non judgemental attitude				

	ATTRIBUTE	RATING (tick ONE box only for each attribute)			
		ALWAYS	USUALLY	SOMETIMES	NEVER
3. CONTEXT	Reviews patient information prior to the consultation				
	Introduces and explains own role				
	Establishes how involved the patient wants to be in decisions about their treatment				
	Clarifies the timing, boundaries and expectations of the consultation				
	Ensures that the consultation takes place in an appropriate setting and minimises interruptions				
	Keeps focused on the agreed aims of the consultation				
4. KNOWLEDGE	Knows own limitations				
	Maintains up-to-date professional knowledge and skills appropriate to own role				
	Knows when and how to seek further advice				
	Refers on to other health professionals and social services as required or as requested				
	Works in partnership with colleagues				
	Shares up-to-date information with patients about specialist support and community resources				
	Is aware of practical resources to help patients				

MANAGING AND SUPPORTING MEDICATION ADHERENCE					
	ATTRIBUTE	**RATING** (tick ONE box only for each attribute)			
		ALWAYS	**USUALLY**	**SOMETIMES**	**NEVER**
5. UNDERSTANDING	Seeks to understand the patient's current circumstances and previous experiences that may impact on treatment				
	Is aware of whether the patient's cultural, religious or societal beliefs impact on treatment				
	Explores what the patient thinks about medicines in general				
	Respects the patient's expertise and knowledge of their condition				
6. EXPLORING	Explores what the patient has been doing to deal with symptoms / illness and what the patient understands about their treatment				
	Discusses with the patient their expectations and concerns about their illness and treatment				
	Provides full, accurate and understandable information about the patient's symptoms / illness and the benefits, effects, risks (e.g. side effects) and uncertainty of all treatment options				
	Discusses prognosis and likely health outcomes				
	Establishes whether the health professional and the patient have similar or different views about the patient's symptoms / illness				
	Discusses any misunderstandings about illness or treatments				
	Encourages the patient to express positive and negative views about treatment and no treatment options				

7. DECIDING	Discusses the patient's preferred option for treatment, negotiates treatment goals and decisions, but accepts the patient's final decision				
	Gives the patient time to consider the information before making a decision, if appropriate				
	Maintains appropriate professional records about decisions that are made and their outcomes				
	Explores the patient's ability to undertake the agreed plan				
	Checks that the patient knows what medicines they are taking and why				
	Discusses when treatment will be reviewed (and what this entails), changed or stopped				
	Ensures that the patient knows what to do if their symptoms change, do not improve, or if a problem arises (e.g. a side effect)				
8. SUPPORTING	Recognises non-adherence (identifies patients at risk of non-adherence, assesses patients' adherence, for example by asking if they have missed any doses of their medication, and recognises the effects of non-adherence)				
	Identifies reasons for / causes of non-adherence, and barriers to future adherence				
	Manages adherence by providing effective practical support where the patient needs / wants help with adherence				
	Supports patients by providing ongoing information and feedback (including encouraging patients to come back with any questions), and monitors adherence				

programmes, to provide training linked to service provision and to provide the link between training and practice. They can be used by individual students and health professionals to assess own performance and identify gaps in knowledge and skills, to identify education, training and professional development needs, and to demonstrate requirements for service delivery. Employers can use them as aids to appraisals and setting personal development plans, to provide opportunities for employers to work collaboratively, to deliver training for staff and to support retention and recruitment. In addition, commissioners can use them to set standards and monitor service delivery, to provide a framework for accreditation of health professionals for service delivery and to identify and remedy poor performance.

The common curriculum included in the educational framework is intended to guide the education and training of health professionals in their work with patients and their medicines. It sets out a series of intended learning outcomes and associated educational content about medication adherence. The curriculum may be adapted for different levels of study and incorporated into existing education and training curricula for health professionals. Specifically, it can be used by education and training providers in the initial education of health professionals and in postgraduate education and training programmes. It can be used to assess own performance and identify gaps in knowledge and skills, and to identify education, training and professional development needs. Regulatory and professional bodies could use it to set standards, to provide a framework for accreditation of health professionals and to identify and remedy poor performance. The educational content outlined in the curriculum may be incorporated into any learning and teaching activities that encourage active student participation including interactive small group workshops, interaction with simulated patients with feedback on performance, case studies, directed and self-directed study, inter-professional learning activities, personal reflections on placement activity.

8.4.5 Main findings and conclusions

The educational framework was distributed to all University schools of pharmacy, medicine and nursing in 16 European countries and a further 70 health profession organisations and federations. The wide distribution and easy availability of the resources is intended to raise standards, ensure consistency of teaching practice across Europe and across professions, and make it much easier for educators to incorporate learning about medication adherence into existing curricula.

8.4.6 Strengths and limitations

The educational framework benefits from having been widely distributed and made easily available; the coverflow PDF version is available from the ABC website for and the iBook version is available from the Applestore. The other key strength of the framework is that is designed to be flexible and adaptable by not being overly prescriptive. This allows it be accessible to a wide audience and future-proofed as far as possible. Limitations to the framework include the low response to consultation, although this does not mean that the response received was not representative of

patients' views, and pharmacy, medicine and nursing in Europe. The other main limitation is that it was not possible to future-proof the reading list.

8.4.7 Implications and recommendations

The educational framework can be used to help ensure that individuals and teams who engage with patients in managing and supporting adherence to medicines possess all the relevant expertise. It can help individuals, and their employers or managers, identify gaps in knowledge and skills and therefore identify ongoing training and development needs. It can inform the commissioning, development, provision and accreditation of appropriate education and training programmes at all levels. As such, we recommend its adoption throughout Europe by health professionals, students, higher educational institutions and training organisations, as well as employers, commissioners, regulators and professional bodies.

8.5 Developing consensus among medication adherence stakeholders on strategies to address patient adherence

8.5.1 Introduction

Many patients do not take prescribed medication as advised[25]: the World Health Organisation[26] reports that only around 50% of the general population in developed countries are adherent to long-term therapies. Non-adherence can have a negative impact on the efficacy of treatments, patient wellbeing and the use of scarce health care resources.[27 28] The importance of finding ways to increasing adherence is highlighted by Haynes and colleagues[29] in a systematic review of adherence interventions: "Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments".

However, this is not simply a matter of patients choosing not to take medicines as prescribed (intentional non-adherence) or experiencing difficulty with taking medicines (non-intentional non-adherence), since there are recognised to be a wide variety of factors that shape the landscape within which patients take medicines.[30-32] These range from factors that are concerned with interactions with health professionals to those that are related to broader societal issues.[30] The interplay between these factors is highly complex and no single intervention or approach has been shown to adequately address all of these issues.[30] Over at least the last three decades a vast but often contradictory body of literature on medicines adherence has accumulated that bears testimony to this.[25 33] As such, numerous gaps in knowledge remain and clear research-based evidence of how to reduce non-adherence on a large scale remains elusive. This suggests that a comprehensive and integrated approach is required to developing an evidence-informed strategy, which includes action at health policy level within and across nations.

One approach that is recognised to be of value in dealing with complex issues like this, where there are known to be numerous highly complex and inter-related factors involved and where uncertainties inevitably remain, is to harness expert opinion through consensus building.[34-37] The Delphi method[34] is used to ascertain expert opinion and build consensus through a series of 'rounds' of structured questioning with feedback at each stage. The technique enables a wide range of expertise on a particular issue to be collated and is ideally suited to electronic group communication when participants are widely geographically dispersed.[38] Participants retain anonymity throughout the Delphi process to minimise the influence of identity in their responses. A Delphi study was used to amass expert opinion on the causes, consequences, and solutions to medication non-adherence across Europe and develop consensus on the relative importance, and operational and political feasibility of potential solutions.

8.5.2 Method

The Delphi Expert Panel

Purposive sampling ensured that potential participants had expertise relevant to one or more of the five dimensions of adherence in the World Health Organisation model.[26] Panel members were sampled from the following five stakeholder groups to ensure a broad range of expertise: academic; healthcare commissioner or policymaker; pharmaceutical industry representative; patient, carer, or patient organisation; healthcare professional. European Medicines Agency representatives were also invited to take part. Participants were nominated by ABC Project researchers or identified through an extensive internet-based search. 50 individuals from 14 countries participated in one or more rounds of the study. There were 25 males and 25 females on the Panel. All five stakeholder groups were represented on the panel and several panellists belonged to more than one group. The European Medicines Agency was also represented.

Study Design

The Delphi study proceeded over a series of four rounds held between January and June 2011. All rounds were completed online using Survey Monkey software and panellists received feedback electronically via blind carbon copied emails. A consensus meeting with ABC project partners and members of the Delphi Panel took place at the end of the study to further develop the policy solutions. The study received ethical approval from the Institution ethical review panel.

The Delphi Rounds

Round 1

Three open-ended questions were presented to the Panel: What do you think the reasons are why people do not take their medicines as prescribed?; What do you think the consequences are of

medicines non-adherence?; What do you think the solutions are to medicines non-adherence? Participants were asked to write as much or as little as they wished in response to each question.

For each of the three questions posed to the Panel in Round 1, the researchers independently segmented each panellist's responses into a series of discrete statements. Statements were then coded and assigned to emerging categories in a series of refinements of the categorisation. Statements that were identical or very similar in essence were collapsed to form a single statement. Validation of the categorisation process involved discussing the features of each category to ensure distinctiveness, establishing agreement that category names reflected the statements that they subsumed, and scrutinising statements that were not initially placed in a category for congruence with existing categories. Some statements were not categorised, including general introductory text around the subject, humorous remarks, and direct repetition of an earlier statement within the participant's response. The researchers remained blind to the authorship of statements throughout.

Round 2

All panellists received feedback on the Panel's responses to the three questions from Round 1 and instructions for the next round. Round 2 focused on the Panel's proposed solutions to non-adherence from the first round by inviting participants to agree, reject, or amend each proposed solution and offer new solutions that had not been advanced in Round 1.

An a priori criterion for refining the solutions specified that those rejected by more than 50 per cent of the Panel should not be taken forward to Round 3. Where amendments were proposed, data from Round 1 were revisited to seek examples, clarification, or support for suggested modifications that could be made without changing the core meaning of statements.

Round 3

Participants received feedback about the panel's collective responses to Round 2 and were asked to rate the importance, and operational and political feasibility of each solution. Ratings were made on five-point Likert-type scales, as shown in Figure 8.5.

There are no definitive guidelines for establishing consensus in Delphi literature. While some researchers have suggested that 51% agreement among respondents can be interpreted as indicating consensus,[38 40] others have adopted more stringent levels.[41] Prior to data collection,[35 42] we defined consensus as 75 per cent or more responses falling within a two-point bracket on a response scale.[43 44] For instance, if 75 per cent or more respondents provided ratings of "3" (somewhat important) or "4" (very important) on the importance scale for a particular solution, this was deemed to represent consensus of the panel on the importance of that solution.

Round 4

The purpose of this round was to seek consensus on ratings which the Panel had not converged in Round 3. Panellists received the potential solutions to non-adherence for which consensus had not

previously been reached, alongside the mean ratings of the Panel from the previous round. Participants who had taken part in Round 3 were also provided with a reminder of their own previous ratings for the potential solutions. Participants were asked to re-rate those particular dimensions for which consensus had not been achieved. All participants were invited to comment on their Round 4 ratings.

Means and standard deviations were calculated for all ratings made across Rounds 3 and 4. To produce a set of solutions to non-adherence that reflected the priorities of the panel, only those solutions considered to be “very important” or “extremely important”, i.e., those with an importance rating of 4.00 or higher, were taken forward to the consensus meeting. Overall priority ratings for these policy solutions were calculated by summing the mean importance score and the average of the two mean feasibility scores for each solution.

Figure 8.5. Response scales used by the Delphi Panel for rating the importance, operational feasibility, and political feasibility of solutions to medication non-adherence

Importance scale	Operational feasibility scale	Political feasibility scale
1. Not at all important - Unlikely to have any impact on non-adherence - Not at all confident about effectiveness of solution - Basic research needed	**1. Definitely unfeasible** - Cannot be implemented - Unprecedented allocation of resources would be needed	**1. Definitely politically unfeasible** - Politically unacceptable - Completely unacceptable to the public
2. Slightly important - Potential for impact on a minority of patients - Not very confident about effectiveness of solution - Major research effort needed	**2. Probably unfeasible** - Some indication that this cannot be implemented - Large scale increase in available resources would be needed	**2. Probably politically unfeasible** - Major political obstacles - Not acceptable to a large proportion of the general public
3. Somewhat important - Potential for impact on some patients - Unsure about effectiveness of solution - Indeterminable research evidence available	**3. May or may not be implemented** - Contradictory evidence that this can be implemented - Increase in available resources would be needed	**3. May or may not be implemented politically** - Political obstacles - Some indication that this may not be acceptable to a large proportion of the general public
4. Very important - Potential for impact on majority of patients - Quite confident about effectiveness of solution - Some research still required	**4. Probably feasible** - Some indication that this could be implemented - Available resources would have to be supplemented	**4. Probably politically feasible** - Some minor political obstacles - Further consideration may have to be given to public reaction, although some evidence exists that the proposed solution may be acceptable
5. Extremely important - Potential for widespread general impact - Very confident about effectiveness of solution - No further research required	**5. Definitely feasible** - Can be implemented - Necessary resources (financial, labour etc) are presently available	**5. Definitely politically feasible** - No major political obstacles - Will be acceptable to the general public

The importance rating scale was adapted from Hardy et al.,[43] while the feasibility scales were adapted from Adler and Ziglio[34].

The Consensus Meeting

A group of 40 Delphi panellists and ABC Project researchers from 10 countries met at the Royal Society, London in June 2011. All stakeholder groups from the Delphi study were represented. The objective of this meeting was to further develop the policy solutions through group discussion. A plenary session at the end of the meeting enabled the chairs of each discussion group to present key outcomes of the roundtable discussions. The discussions were audio-recorded with participants' consent.

The recordings of the plenary sessions were transcribed verbatim and analysed by two researchers who had not participated in the discussions. Key themes, ideas, and recommendations for policy development were extracted. The policy solutions were amended in light of the recommendations for development that had been agreed within participants' discussions.

8.5.3 Results

Round 1

The three questions generated a total of 1,142 statements; 531 statements in response to question 1, 256 for question 2, and 355 statements in response to question 3, from which 501, 244 and 343 statements, respectively, were extracted for analysis.

Causes of non-adherence to medication

Approximately 43% of the causes of non-adherence concerned aspects of patients' behaviour, beliefs or characteristics. These included forgetfulness, low health literacy, and negative beliefs about medicines. Patients' experience and interpretation of treatment, such as perceptions of feeling no benefit from treatment and, conversely, stopping treatment when benefit was experienced, were also perceived as causes of non-adherence. Medication itself was a cause of non-adherence in nearly 20% of statements, because of the complexity of medication regimens, polypharmacy, the cost of medication for the patient, and side effects. Overarching theories about the causes of medicines non-adherence represented a significant minority of statements. These often referred to the multiplicity of factors that together can result in non-adherence, and the notion that medicines non-adherence can be intentional and unintentional.

Consequences of non-adherence to medication

Panellists viewed the consequences of medication non-adherence to be overwhelmingly, but not exclusively, negative. Over half of the consequences listed by the Panel were experienced directly by the patient, positive or negative, through symptom experience, disease progression, quality of life, illness and death. A quarter were experienced by the healthcare system, through waste of money, medication and resources and increased utilisation of healthcare.

Although the consequences of medication non-adherence were largely perceived as negative by the panel, positive consequences of medication non-adherence were also listed. Positive consequences for patients included the avoidance of adverse/side effects resulting from medication use. Patient quality of life was also seen to benefit from medication non-adherence through feeling that one is not dependent on medication, and feelings of control and mastery.

Table 8.1. Causes of medication non-adherence by category

Category	Count	%
Patient factors - patient behaviour/characteristics	100	20.0
Medication factors	98	19.6
Patient factors - treatment effects	66	13.2
Patient factors - patient beliefs and concerns	55	10.9
Clinician factors	42	8.4
Meta theories of adherence/ theories of adherence	42	8.4
Healthcare organisation factors	32	6.4
Patient/clinician interaction	29	5.8
Environmental and social/structural factors	28	5.6
Disease factors	9	1.8
Total	501	

Table 8.2. Consequences of medication non-adherence by category

Categories	Number	%
Themes/theories	20	8.2
Consequences for patients	125	51.2
Disease consequences	*54*	
Medication consequences	*46*	
Quality of life/well-being consequences	*25*	
Consequences for healthcare professionals	6	2.5
Consequences for clinician-patient interaction	11	4.5
Consequences for the healthcare system	62	25.4
Waste of resources	*52*	
Public health risk	*10*	
Consequences for society	20	8.2
Waste of resources	*14*	
Research/industry	*6*	
Total	244	

Solutions to non-adherence to medication

More than half of the solutions offered by panellists focused on achieving change in patients' knowledge and behaviour. There were nearly three times the number of statements relating to changing or adapting patients' knowledge and behaviour than those relating to changing or adapting healthcare professionals' education and behaviour. Solutions focusing on change at the healthcare system or government level together amounted to less than 10% of the solutions generated by the panel.

A substantial proportion of statements by panel members emphasised the need to improve patient education and information about treatment to make the information understandable, impartial, evidence-based, and inclusive of details of other forms of treatment. A similar number of statements described improving education and information about the administration of medication. Several statements specified the need to improve education and information on the potential side effects of the medication, while others expressed the importance of improving education and information to inform patients' risk-benefit analysis.

A sub-set of solutions related to changes to medication, including simplification of the regimen, the development of better drugs with reduced side-effects, and improved packaging and often referred to the tailoring of dosage to individual need and to compatibility with the patient's lifestyle.

Improving education and training for identifying and assessing medication non-adherence was a prominent solution for the panel. A number of statements focused on improving education and training in patient-centred care to move away from a paternalistic approach to patients. A large number of statements about the input of healthcare professionals related to the provision of ongoing feedback and support with medication-taking. Frequently cited amongst the healthcare professional-focused solutions was the importance of taking a non-judgmental approach and ending the conception of non-adherence as something that should be blamed on patients. The final category of solutions pertaining to healthcare professionals was the use of reviews of medication and included suggestions such as targeting reviews towards patients on multiple medications or complex regimens.

Solutions concerning clinician-patient interaction were fewer in number than those relating to healthcare professionals. Ensuring patient involvement and a partnership approach between clinicians and patients, building a partnership between doctors and patients, and the provision of frequent opportunities for open discussion with the patient about medication-taking were frequent statements here. The need to discuss patients' beliefs about medications, the condition, and the likelihood of taking medications was also expressed. Statements about discussing patient preferences formed another category.

Table 8.3. Solutions to medication non-adherence by category

Solution Category	Number	%
Patient focused solutions	187	54.5
Educational/informational	*107*	
Medication-related	*39*	
Behavioural strategies to eradicate forgetfulness etc.	*32*	
Involvement of the social network/caregivers can support patients with medication adherence	*6*	
Building the patient's trust in the healthcare professional would improve medication adherence	*3*	
Healthcare professional focused solutions	69	20.1
Clinician-patient interaction focused solutions	43	12.5
Themes/theories relating to solutions	16	4.7
Health system solutions	14	4.1
Government focused solutions	14	4.1
Total	343	

A small number of solutions referred to the impact of the health system on adherence behaviour and these fell into four categories. The first was a team approach to treatment by healthcare professionals, for example, the involvement of nurses and pharmacists, and the concept of the 'Medicine Education Team'. The second category concerned financial investment for supporting adherence. The last two categories within the scope of the healthcare system are in opposition; while the larger of the two contained statements about reducing the cost of medications for patients through the development of reimbursement systems, removing prescription charges, and lowering out of pocket costs for medication, the other encompassed statements about financial penalties for the non-adherent patient.

A few solutions related to government involvement in adherence support. Three categories emerged: statements relating to the investment of resources or money in medication adherence, particularly regarding education, research, and access to medicines; increasing public awareness of the issue of medication adherence, for instance through public education campaigns and interventions to improve health literacy; and suggestions for policy development in the field of adherence, for example, elevating patient adherence as a critical healthcare issue.

Three overarching themes on solutions to non-adherence emerged from the data. These were not solutions but rather 'meta-theories' about the nature of solutions to non-adherence. The most commonly cited theme related to the complex nature of solutions and the need for multifaceted interventions to achieve a comprehensive response to non-adherence. Several panellists also highlighted the lack of long-term effectiveness of current solutions to non-adherence, and the absence of an evidence base for the effectiveness of adherence interventions. The final theme was the need for solutions to correspond to reasons for non-adherence, for example, developing solutions matched to unintentional or intentional causes of non-adherence.

Round 2

For each of the 43 proposed solutions presented in Round 2, the percentage of the panel that agreed with, rejected, or amended the solution was calculated. Two solutions that did not meet our a priori criterion for inclusion were deleted.

Round 3

The panel achieved consensus for 64 of the 126 ratings. One solution was removed following feedback from panellists.

Round 4

Means and standard deviations for the 60 ratings that were made in Round 4 were calculated. The same criterion for determining consensus used in Round 3 was used in Round 4 to determine consensus (75% of ratings falling within a two-point bracket on the response scale). A substantial shift towards convergence of ratings was found, with 58 of the 60 ratings achieving consensus. Overall, 121 of the 123 ratings made across Rounds 3 and 4 achieved consensus.

Prioritised solutions were identified and ranked in a two-step process. Only those solutions considered to be "very important" or "extremely important" by the Expert Panel (i.e., with a mean rating of 4.00 or higher) were retained. The application of this criterion resulted in 25 policy solutions remaining in the final list. In order to determine the level of priority of each of these 25 solutions, the importance and feasibility ratings were combined in a single score by summing the mean importance score and the average of the two mean feasibility scores for each solution, as shown in Table 8.4.

Consensus meeting

Minor amendments were made to the wording of policy solutions on the basis of themes identified from transcripts of final plenary statements at the consensus meeting and from discussion with the wider ABC project team. The resulting dissemination statement of consensus-based policy solutions for medication adherence is shown in Figure 8.6.

Table 8.4. The ABC Delphi Panel Medication Adherence Policy Solutions

Policy solutions	Priority rating*	Mean importance♦	Mean operational feasibility	Mean political feasibility
1. Improve patient education and information when a medication is newly prescribed	8.92	4.47	4.39	4.50
2. Improve patient education and information focused on the patients' treatment	8.42	4.13	4.16	4.42
3. Improve patient education and information regarding the benefits of adherence to their particular medication(s)	8.40	4.11	4.24	4.34
4. Improve education and training for healthcare professionals about ways of addressing medication non-adherence to drive improvements in clinical practice	8.32	4.42	3.86	3.93
5. The patients' preferences for treatment should be discussed to support medication adherence	8.27	4.32	3.89	4.00
6. Improve education and training for healthcare professionals about patient-centred care	8.25	4.32	3.89	3.96
7. Improve patient education and information about potential side effects or adverse effects and how to manage them	8.21	4.08	4.13	4.13
8. Healthcare professionals should support patients with concerns about or experience of side effects of medication	8.18	4.18	3.96	4.04
9. Improve education and training for healthcare professionals about identifying and assessing medication non-adherence to drive improvements in clinical practice	8.06	4.18	3.76	4.00
10. Ensure patient involvement and a partnership approach, for example in treatment plans and decisions, to support medication adherence for those	8.05	4.32	3.66	3.79

patients who wish to be involved				
11. Simplify the patients' medication regimen (e.g., less frequent, modified formulation and/or dosage, tailored to individual need)	8.05	4.16	3.82	3.96
12. Improve education and training for healthcare professionals regarding medication adherence in general	8.03	4.05	3.95	4.00
13. Improve patient education and information to assist the patient to weigh up the benefit and harm of medication	7.99	4.18	3.75	3.86
14. Increase public awareness of the issue of medication adherence	7.94	4.13	3.82	3.79
15. The patients' health- and medication-related beliefs should be discussed between the clinician and the patient to support medication adherence	7.90	4.29	3.50	3.71
16. Healthcare professionals should use reviews of medication to discuss medication adherence with patients	7.84	4.03	3.82	3.79
17. Healthcare professionals should provide the patient with ongoing feedback and support with medication-taking	7.82	4.07	3.79	3.71
18. Stop medication(s) that the patient no longer needs or wants	7.81	4.00	3.75	3.86
19. Ensure a consistent team approach to treatment, in which all members of the healthcare team work together to support medication adherence	7.61	4.21	3.18	3.61
20. Healthcare professionals should adopt a non-judgmental approach to the issue of medication adherence	7.61	4.11	3.43	3.57
21. Build patients' trust in the healthcare professional to support medication adherence	7.60	4.11	3.43	3.54
22. Information provision should be tailored to the individual preferences or	7.56	4.03	3.34	3.71

needs of the patient				
23. Governments should implement evidence-based policies about medication adherence	7.53	4.05	3.42	3.53
24. Governments should invest resources/money in medication adherence, particularly regarding education, research, and access to medicines	7.39	4.11	3.34	3.21
25. Healthcare professionals should make sufficient time for the patient, for instance through more frequent contact	6.79	4.00	2.76	2.82

* Higher ratings indicate higher priority; lowest possible priority rating = 2, highest possible priority rating = 10

Figure 8.6. ABC consensus-based policy solutions for medication adherence for Europe

Patients benefit when provided with support, education, and information
- when a medication is newly prescribed
- focused on the patients' treatment
- about the benefits of adherence to their particular medication(s)
- about potential side effects or adverse effects and how to manage them
- to assist the patient to weigh up the benefit and harm of medication
- tailored to the individual preferences or needs of the patient

Healthcare professionals should receive education and training about
- patient-centred care
- identifying and assessing medication non-adherence
- ways of addressing medication non-adherence when it is identified

so that they can:
- adopt a non-judgmental approach
- identify medication non-adherence
- provide patients with ongoing feedback and support with medication-taking
- support patients with concerns about, or experience of, side effects of medication
- make sufficient time for the patient, for instance through more frequent, timely contact

Together, healthcare professionals and patients should
- discuss the patients' preferences for treatment
- ensure a partnership approach in decision making and treatment
- discuss the patients' health- and medication-related beliefs
- build the patients' trust in the healthcare professional

Regarding medicines
- simplify the patients' medication regimen as appropriate (e.g., less frequent, modified formulation and/or dosage, tailored to individual need)
- stop medication(s) that the patient no longer needs or wants

Healthcare providers should
- promote a team approach, sharing information to deliver consistent adherence support
- prioritise medication adherence support in service, organisation, and systems design

Governments/healthcare payers should
- increase public awareness of medication adherence for all citizens
- develop and implement evidence-based interventions for medication adherence
- provide training and guidance for all healthcare providers so they can deliver effective adherence interventions
- invest in research to identify effective interventions demonstrating value for money

8.5.4 Discussion

8.5.5 Main findings and conclusions

The Delphi panellists achieved consensus about a broad range of policy solutions for Europe to address medication non-adherence, and agreed on the relative importance and feasibility of those solutions. This consensus is all the more significant having been obtained with participants from fourteen countries from a diverse range of stakeholder groups who might be expected to have divergent perspectives, experiences and interests in medication adherence. Participation in a Delphi study demands a significant commitment of time and effort over a number of months and the 1,142 separate statements made by this Panel represent a significant resource.

8.5.6 Strengths and limitations

Many, but not all, of the solutions target action at the patient and the public, rather than policy interventions at the healthcare provider or systems level. This may well correspond with the Panels' beliefs, reflected in the wider research literature that the primary cause of non-adherence is patient's beliefs about illness and treatment.[45 46] Equally, the majority of published adherence interventions are educational and behavioural interventions to change patient behaviour rather than (potentially more challenging) interventions to change healthcare systems and culture.[15] When considering potential solutions to non-adherence, panellists may have brought to mind those causes and interventions for non-adherence with which they are most familiar from research literature and practice, hence the focus on patient-oriented solutions over other ways of intervening to address medicines non-adherence.

For the purpose of this task, Panellists were instructed to think about each potential solution, and in later rounds, the importance and feasibility of each solution, in isolation. In practice, interventions to support medicines adherence may be multi-faceted, delivered in parallel, and cut across the categories used here to help structure the task for participants. This study does not tell us how policy makers and commissioners might seek to combine interventions for best effect or perhaps stagger the introduction of individual solutions within an overall implementation strategy.

Nevertheless, this study improves on previous research initiatives to develop policy recommendations for medicines adherence in several ways. The policy solutions represent the combined views of a diverse group with a remit for adherence, rather than the views of a specific interest group or a single professional group.[47 48] The proposed solutions also look beyond the actions and interactions that occur in the clinical setting[7] to broader systems and process factors that impact on medicines adherence. Recommendations for policy to address medication adherence identified here for Europe are similar in scope to policy initiatives in the USA,[49 50] which have also been developed with multi-stakeholder input.

Other research in this area, such as systematic reviews of adherence interventions,[29] tends to report that the evidence for the effectiveness of adherence interventions is either limited, short lived in duration of effect, or both. Many adherence interventions in research studies are complex and it can be difficult to tease apart the active ingredients of the intervention. A challenge for healthcare policymakers is overcoming the stark gap between interventions that are delivered as part of clinical trials and the reality of what is possible in clinical practice and within limited budgets. This study provides succour for the policy maker seeking effective solutions for medicines non-adherence that are also feasible at an operational and political level. On the latter point, the research evidence-base has little to offer. In this regard our study may act as a guide for evidence-informed implementation.

8.5.7 Implications and recommendations

The consensus-based solutions to medication non-adherence for Europe are broad in nature. The breadth of the policy solutions enables significant flexibility in national implementation to reflect differences in healthcare systems, health-related culture, available resources, and the level and sophistication of existing implementation. Local implementation of the highest priority item 'improve patient and education when a medication is newly prescribed' could, for example, be delivered in a number of ways: as part of a community pharmacy service such as the New Medicines Service in England;[51] in conjunction with a trial prescription programme such as those in Canada;[52] or within the context of existing services provided in primary care. The policy solutions described in Figure 8.6 have sufficient flexibility to incorporate a number of implementation responses. Future efforts should focus on sharing implementation practice to improve our knowledge of the range of policy responses to medication non-adherence across Europe.

8.6 Implementation of medication adherence policy solutions: How do European countries compare?

8.6.1 Introduction

In the previous section of this chapter, we reported that a panel of experts belonging to various stakeholder groups from Europe and further afield took part in an online Delphi study and consensus meeting. The aim of the study was to generate solutions to non-adherence and reach consensus on their importance, operational feasibility, and political feasibility. This research resulted in 26 consensus-based policy recommendations, deemed by the panel to be high priority, for addressing medication non-adherence across Europe.

Here we describe a subsequent study to explore the perceptions of medicines policymakers of the extent of implementation of those 26 consensus-based policy solutions, within member states of the European Union (as shown in Figure 8.6).

Specifically we set out to explore:

1. The extent to which each of the 26 consensus-based policy solutions had been implemented in European countries.
2. Where countries have implemented one or more of the policy solutions, to obtain information on any benefits and costs resulting from implementation.
3 Perceptions of the appropriateness of current levels of implementation.
4. Where countries have not implemented the policy solutions, to determine whether the recommendations will feature in future planning to address non-adherence to medication.
5. Any perceived barriers to implementing the policy solutions within countries.
6. The views of medicines policymakers about the comprehensiveness and fit of the 26 policy solutions for their country.

8.6.2 Method

Participants

Purposive sampling was used to identify the National Lead with responsibility for medicines policy, including adherence to medication, in each of the 27 member states of the European Union. National Leads were contacted through correspondence with National Ministries of Health, National Medicines Authorities or Agencies, and representatives of the European Medicines Agency. National Leads who were unable to take part in the study were invited to nominate their deputies to participate (all participants are referred to as National Leads throughout this chapter). During the process of sampling it became apparent that responsibility for policy on adherence was often distributed across various individuals, departments, and even authorities. In these cases, National Leads were invited to refer questions to colleagues if they did not feel well-placed to respond. Of the 27 National Leads invited to participate in the study, 10 (Bulgaria, Denmark, Estonia, Finland, Germany, Ireland, Latvia, Lithuania, Malta, and The Netherlands) completed the self-assessment survey and seven (Estonia, Finland, Germany, Ireland, Lithuania, Malta, and The Netherlands) engaged in a follow-up interview. All components of the study were conducted in the English language.

Design

A mixed-methods design was employed. A cross-sectional online survey was administered through Survey Monkey software in the first phase of the study and semi-structured telephone interviews were conducted in the second phase.

Measures

Participant details

Each participant was asked to provide details of their job title, organisation, nationality, and email address.

Self-assessment survey

The self-assessment survey was designed to enable quantitative assessment of each country's own policies on medication adherence in relation to the ABC consensus-based policy solutions. The measure was structured around the 26 policy solutions for medication adherence developed through the aforementioned Delphi study and consensus meeting. Policy solutions were presented in the following categories, according to the main target of action: patient-focused, healthcare professional-focused, clinician-patient interaction-focused, health system-focused and government-focused solutions. Participants were asked to rate each policy solution on two scales. The first scale assessed the extent to which each policy solution had been implemented in the respondent's nation, using a five-point Likert-type response scale anchored by *"Discussed and considered but not implemented"* (1) and *"Fully implemented in all regions for all health conditions"* (5). The second scale measured participants' perceptions of appropriateness of the level of implementation for each policy solution. Ratings were made on a five-point Likert-type response scale anchored by *"Far too little implementation"* (1) and *"Far too much implementation"* (5) as shown in Figure 1. These scales were adapted from the medication self-assessment scale of the Institute for Safe Medication Practices.[53]

Figure 8.7. Response scales for survey questions

1. To what extent has this policy solution been implemented in your nation?

There has been no activity to implement this item	Discussed and considered but has not been implemented	Partially implemented in some or all regions or health conditions	Fully implemented in some regions or some health conditions	Fully implemented in all regions for all health conditions
1	2	3	4	5

2. In your view, does your nation have the appropriate level of implementation of this policy solution (that is, the right level of services, support, resources) for your nation?

Far too little implementation	Slightly too little implementation	About the right level of implementation	Slightly too much implementation	Far too much implementation
1	2	3	4	5

Interview schedule

The interview schedule (see Appendix 8.3) was developed to further explore participants' responses to the self-assessment survey and to identify examples of best practice for adherence to medication

in each of the countries. A semi-structured approach was taken to ensure a degree of standardisation across the interviews whilst also allowing participants to raise other issues, ideas or concerns.[54] The main objective of the interviews was to gather richer information on how the ABC policy solutions compared with existing services and provision in each of the countries. Questions focused on eliciting examples of activities to support adherence within the various categories, participants' decision-making processes regarding implementation of particular policies, barriers to implementation, consequences of implementation, and future planning for medication adherence. Each participant was also asked about models of best practice for supporting adherence within their nation and their impressions of the ABC Project policy solutions. Although a number of key questions were posed to each National Lead, for instance regarding models of best practice for medication adherence, the interview schedule was tailored to each participant according to their survey responses. For instance, if a National Lead had indicated that a particular policy solution had been implemented within their country, a question on the benefits of implementation was incorporated within the interview schedule. Interviews proceeded systematically, addressing each category of policy solution in turn before moving to more general questions about best practices for medication adherence and impressions of the ABC consensus-based policy solutions.

Procedure

Ethical approval for the study was secured from the institutional ethical review panel. National Leads were invited to participate in the study through email correspondence. Each National Lead received a letter of invitation, a participant information sheet, a letter of support for the study from the Chief Pharmaceutical Officer of England, and a briefing document detailing the methods and results of the Delphi study. Prospective participants were invited to contact the researchers with any queries about the study or if they required any further information. All participants were informed that their anonymity could not be guaranteed because of the specificity of the sample. Participants were assured that they would be offered the opportunity to view drafts of any manuscripts containing their data and request amendments. Upon entering the survey, participants responded to three informed consent questions regarding their participation in the survey. Participants were also asked to indicate their consent to take part in a follow-up interview. Those who consented to engage in a follow-up interview were asked a series of questions about the recording of their interview and the use of quotations from interview transcripts.

Following the provision of consent, participants were presented with instructions for completing the self-assessment survey and proceeded to rate each policy solution. After completion of the survey, participants received a feedback document containing details of their ratings. Those who had consented to engage in a follow-up interview received a copy of the interview schedule and were asked to indicate their availability for interview. Where possible, interviews were conducted within two weeks of participants completing the survey. All interviews were conducted by two researchers over the telephone and lasted between twenty minutes and an hour. Six National Leads consented to the recording of their interviews and one gave permission for detailed notes to be taken.

Data analysis

Self-assessment survey data

The quantitative data gathered through the survey were collapsed across categories of policy solution. Mean substitution was used to replace missing data. Summary descriptive data were produced for each category of policy solution in each country in order to draw cross-country comparisons on level of implementation and perceived appropriateness of implementation.

Interview data

The qualitative data comprised interview transcripts and detailed field notes. Each transcript or set of field notes was summarised and sent electronically to the appropriate National Lead. National Leads were asked to check that the summary provided an accurate reflection of the interview discussion and invited to add to or amend the content. The finalised and approved interview summaries were used as the basis for data analysis. Data analysis proceeded in an inductive and iterative fashion. Following the approach of Lavis and colleagues,[55] themes were identified using the constant comparative method of analysis. The researchers read interview transcripts as they became available and met regularly to discuss themes and issues arising from the data. A two-stage fragmenting and connecting procedure[56] was employed during analysis. Initially, individual themes were extracted from the data. These themes were then compared both within and across interviews to explore the similarities and differences in services and provision between countries. In addition to facilitating comparisons between countries, this approach enabled modification of the interview schedule in light of new themes and ideas arising from the data.

8.6.3 Results

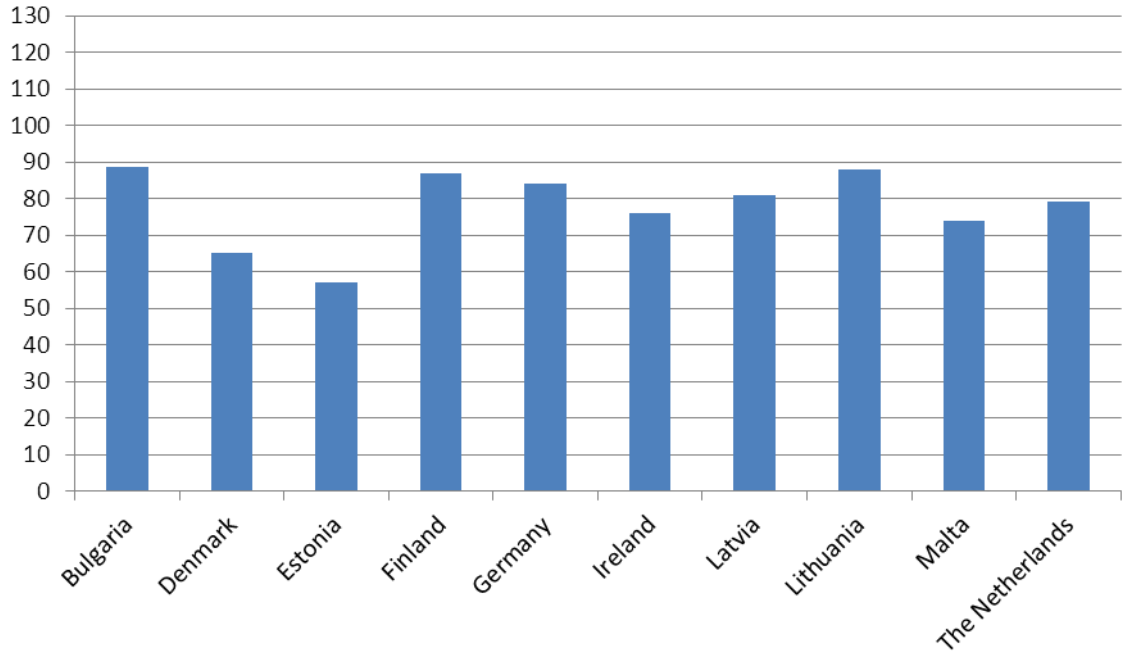
8.6.3.1 Survey data

The mean implementation scores across countries for each category of policy solution indicated that most implementation had taken place at the patient level including, for example, the provision of support, education and information about newly prescribed medicines and the benefits of adherence. This was followed closely by activity focused on improving patient-clinician interactions, for instance through the implementation of a partnership approach. The lowest amount of activity was reported for policy solutions at the government or healthcare payer level, which included investment in research to identify effective interventions demonstrating value for money and increasing public awareness of medication adherence. For all six categories of policy solutions, the mean rating for perceived appropriateness of level of implementation fell below 3.00, indicating that across the ten European countries in the survey, National Leads felt insufficient implementation had taken place for medication adherence in all policy areas.

The mean level of implementation and perceived appropriateness of implementation for each category of policy solution are shown for each of the 10 countries in Figure 8.9. The mean ratings of perceived appropriateness of implementation are below the midpoint for 52 of the 60 scores,

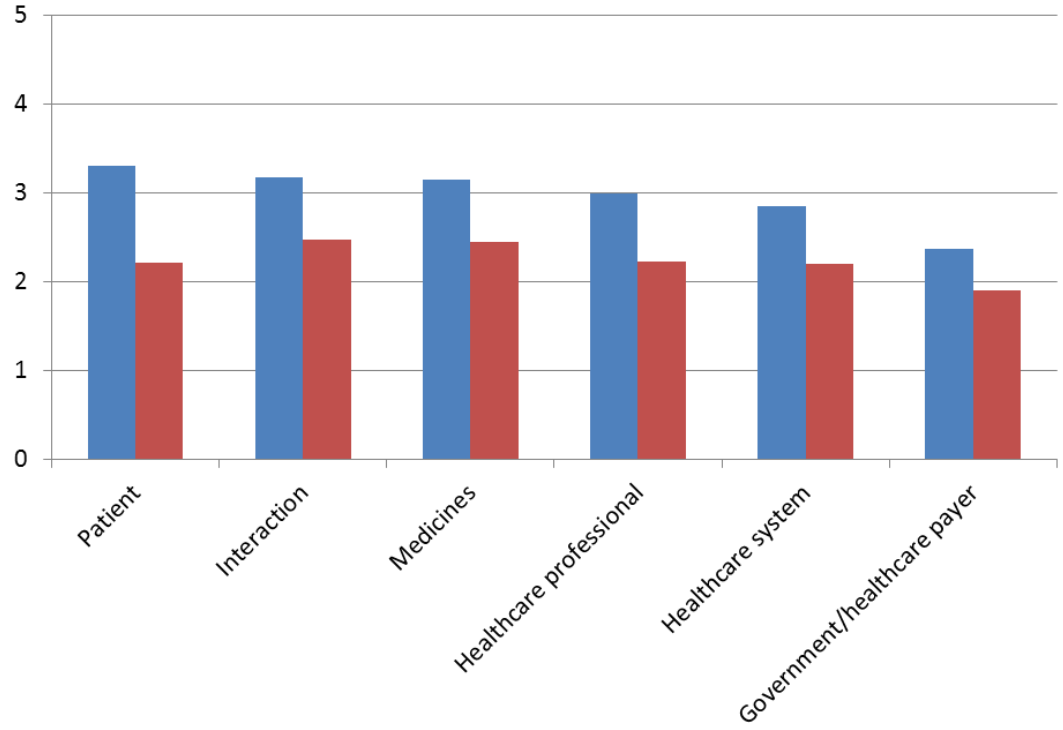
suggesting that the majority of National Leads felt that more could or should be done to support patients with adherence to medication within their nations, across target areas.

Figure 8.7. Total policy implementation score for each country (minimum possible score = 26; maximum possible score = 130).



The mean total implementation rating for the 26 policy solutions across the 10 participating countries was 77.97 (SD = 10.38; range 26-130). Bulgaria attained the highest overall level of self-assessed implementation and Estonia provided the lowest total implementation rating. Figure 8.9 illustrates the variability across countries in total medication adherence policy implementation.

Figure 8.8. Mean implementation and perceived appropriateness of implementation across country for each category of policy solution.



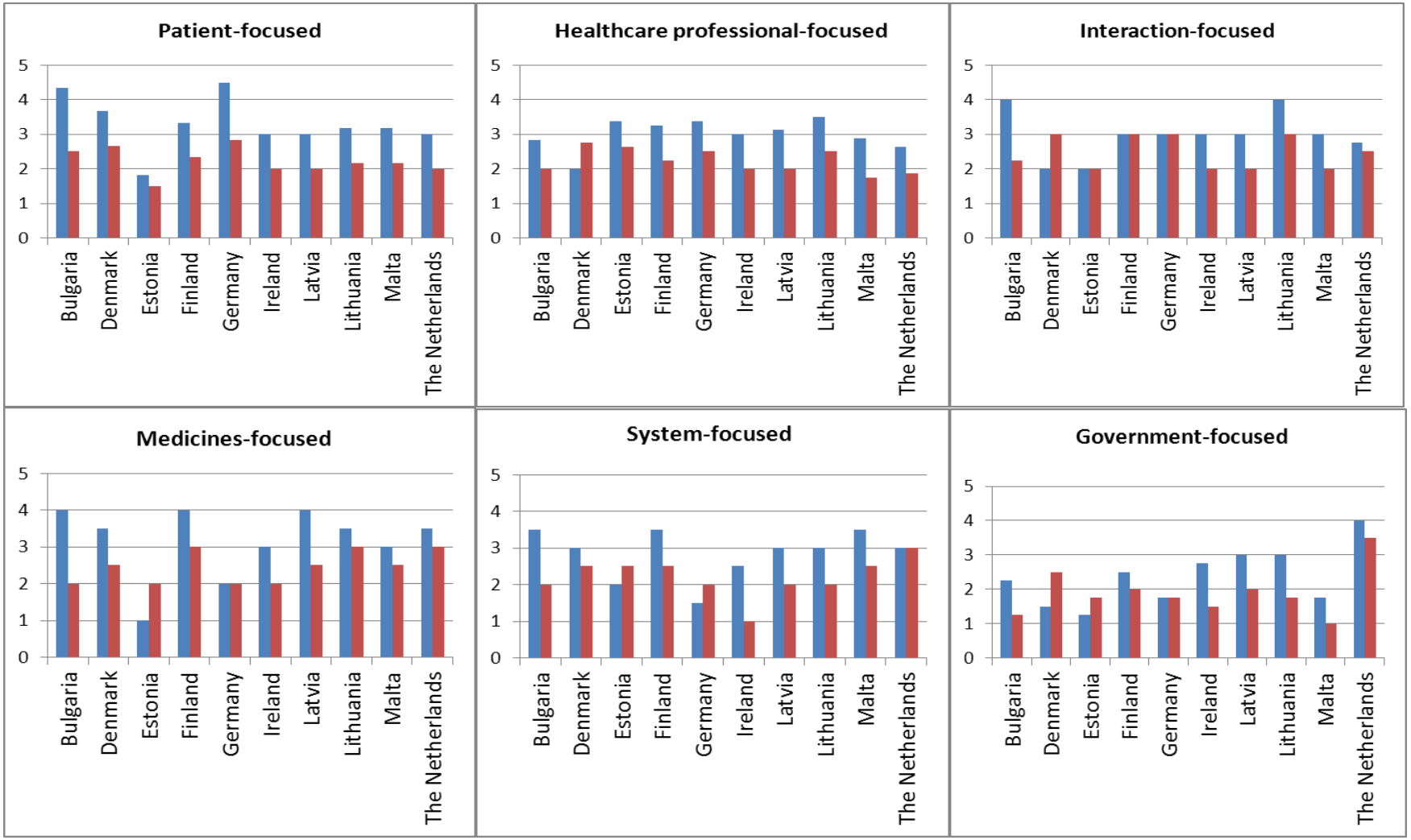


Figure 8.9. Mean implementation and perceived appropriateness of implementation of policy solutions for medication adherence, by category and country

8.6.3.2 Interview data

A range of themes around medication adherence emerged from the interview data, in addition to interviewees' comments about the comprehensiveness of the policy solutions and examples of best practice for adherence. The majority of themes were present across the data of two or more interviewees. Outlines of these themes are presented below. Key differences between nations with high and low levels of implementation activity are shown in Figure 8.10.

Figure 8.10. Comparison of exemplar nation with more activity for adherence with exemplar of nation with less activity

Exemplar of nations with more activity for adherence	Exemplar of nations with less activity for adherence
• Identification of medication adherence as a priority • Structured policy forum for adherence • Involvement of all stakeholder groups • History of activity for adherence • Government investment in initiatives for adherence • Culture of patient-centred care	• Medication adherence not identified as a priority • No structured policy forum for policy on adherence • No coordinated action for adherence • Other issues prioritised above adherence • No government investment in activity for adherence • Healthcare provider-centred approach

Responsibility for medicines adherence policy and planning – meta level

Four nations (Finland, Germany, Malta and the Netherlands) described shared responsibility for adherence policy and planning at the higher level. The particular parties involved differed between the nations. Within the Netherlands, for example, the role of the government was described as a systems approach; ensuring good openings for adherence within the health system and removing obstacles. The policy lead in this nation explained that activity was implemented on a regional basis, as solutions were differentially effective in different regions. Healthcare insurers were portrayed as well placed to influence the behaviour of healthcare providers and patients with regard to adherence. An official working group for adherence, consisting of doctors, nurses, pharmacists, patients, insurers and researchers, was seen as integral to adherence implementation in the Netherlands.

Absence of adherence "theme" in policy documents and practice

Six interviewees emphasised the "hidden" nature of adherence in both policy and practice. Several interviewees stated that policy documents in their nations did make reference to adherence, but these references were often distributed amongst a number of other topics, such as patient safety, rather than falling under the discrete label of "medication adherence". This reduced the visibility of medicines adherence as a focus in policy activity.

Making the case for investment

Two of the policy leads indicated that the area of medication adherence was overshadowed by more pressing issues, such as the availability of medicines, or subject to competition for funding from other medicines-related topics.

The policy lead for adherence in the Netherlands explained that the decision to invest in services for adherence had been simple, and cited the World Health Organisation's (2003) report on adherence to long-term therapies as a prompt.

"It was really quite simple because there was this WHO report about adherence… and it said that about 50% of chronically ill patients didn't use their medicines as they were supposed to be used and when you see how much we pay for medicines in the healthcare system and then you say well, we throw away 50% of this; that's quite a sum! … Yes, and that's really what made the case here to have investments in this area. And we still invest in this area...but on a nationwide scale, not a regional or local one." Netherlands, 97-107.

In two other countries, the case for investment was less straightforward. Interviewees in Estonia and Germany indicated that a lack of money and resources presented significant barriers to implementing initiatives for adherence, even when strong proposals were in place.

Evaluating options and assessing outcomes

Three interviewees described difficulties in deciding which particular initiatives to implement. The policy lead for the Netherlands stated that some initiatives have clearly deserved government support, while decisions for other initiatives were less clear-cut. Issues relevant to these decisions included the scope of expected benefit in terms of widespread or localised effect, the expense of the initiative, and support from doctors or pharmacists. Interviewees in Estonia and Finland emphasised the need for research to identify effective and cost-effective interventions.

Interviewees for Finland, Germany, Ireland, Lithuania and the Netherlands outlined the complexities of evaluating outcomes or benefits of initiatives for adherence. Specific problems included establishing objective, relevant and independent assessment methods. Barriers to evaluation were discussed, such as shortages in time, resources, skills, and other competing priorities. A lack of studies evaluating the outcomes of initiatives was also raised as a problem. The policy lead for Finland highlighted the difficulty involved with identifying improvements in medication adherence, particularly as improvements in health outcomes cannot necessarily be attributed to increased adherence.

Variability in provision and the targeting of resources

Policy leads in Finland, Lithuania and Malta described variability, both planned and unplanned, in provision for medication adherence across different areas of practice and patient groups. In Finland,

adherence was reported to be addressed more thoroughly in patients with long-term conditions, such as cardiac disease, diabetes and asthma, as these patients tend to meet with their doctors more frequently than other patients. The policy lead for adherence in Malta contrasted areas of excellence, for instance specialist teams where there is good communication between healthcare professionals and patients, strong collaboration between various healthcare professions, and detailed information available on the patient's history, with the general system, in which time and support for the patient are more limited.

Interviewees in Finland, Ireland, Malta and the Netherlands referred to the targeting of resources and services. One strategy for targeted adherence support was a focus on patient groups with the more prevalent long-term conditions, for example diabetes and asthma. Targeted support for adherence in the Netherlands focused particularly on conditions where medicines adherence can be more difficult, such as schizophrenia and asthma. Interviewees in Ireland and Malta reported the targeting of some initiatives, for example medication review in Ireland, to particular clinical areas or to patients on complex regimes and/or with comorbidities. The targeting of services towards patients prescribed certain medicines, such as those needing regular monitoring, was also detailed by the policy lead for Malta.

Barriers to implementation

Interviewees mentioned a number of barriers to the implementation of policy solutions for medication adherence. Some of these barriers were common to several countries. A lack of resources and difficulty with financing activity for adherence were reported for Estonia, Finland and Ireland. The need to ensure acceptance of the policy solutions and openness to patient-centred approaches were mentioned by interviewees for Estonia and Malta. Other barriers to implementation included delay and procrastination, shortages in doctors and healthcare centres, the difficulty of implementing best practice developed in one region in another region, and a lack of awareness in the general public with regard to aspects of medicines use. The challenge of achieving a balance between enforcement of policy and practicable implementation was described by the policy lead for Malta.

The impact of major health system changes on adherence

Three interviewees described the indirect effects of broad, health system reforms on implementation of medicines adherence initiatives. Major changes to the healthcare systems over recent years were described for each of these countries. Reforms in the Netherlands included increasing the role of healthcare insurers in designing pharmaceutical care. A radical overhaul of the healthcare system was reported for Ireland, and effects were described as filtering down to impact a variety of domains, including adherence. Reforms in this nation also affected regulatory bodies and the education and training of healthcare professionals. The policy lead in Malta indicated that organisational changes offered a good opportunity to implement new standards for the use of medicines. The policy lead for Ireland referred to European Union initiatives, such as requirements for patient information, which may positively impact support for adherence in individual nations.

Responsibility for adherence – patient level

Consistent with interviewees' comments regarding responsibility and planning at the higher level, responsibility for adherence-focused activity at the patient level was also reported as shared across a number of stakeholders. The policy lead in the Netherlands emphasised the responsibility of "the triangle" – doctors, pharmacists and patients – in making progress on adherence. Interviewees in Finland, Germany, Ireland, Lithuania and Malta also referred to obligations on doctors and pharmacists to produce and deliver patient information; not restricted to but including that on adherence. The involvement of patient organisations in the provision of patient information was outlined by the policy leads for Estonia, Finland, Germany and Malta, while the leads for Estonia and Finland additionally acknowledged the role played by the pharmaceutical industry in funding or collaborating with patient organisations. The policy lead for Finland also mentioned the importance of expert nurses in assisting patients with adherence to medication. Appendix 8.4 includes examples of service provision to support medication adherence mentioned by the medicines policy leads.

Healthcare professionals' training and education

Policy leads in Finland, Ireland and Malta indicated that training and education on adherence to medication in their nations was especially well developed for pharmacists. In addition to content on adherence within the curricula of pharmacy courses, the National Lead for Malta explained that adherence is also covered within voluntary continuing professional education offered by the College of Pharmacy Practice. The interviewee in Ireland described a heavy emphasis on medication adherence in the training of pharmacists, particularly with regard to antibiotics, antidepressants and anti-rejection therapy. Finland's policy lead reported a drive towards campaigns to educate pharmacists on how to improve medication adherence.

The policy leads in Germany, Ireland and Malta all referred to the role of continuing professional development in education and training on adherence. Practice learning under the supervision of a tutor was also mentioned as occurring within Ireland. The interviewees in Germany and Ireland, as well as Lithuania, discussed healthcare professionals' training in methods that may promote adherence, such as patient-centred care and developing a partnership approach with patients. Interviewees also outlined some recent advances in training and education on adherence, such as doctors and nurses taking more credits on aspects of medicines use in Malta and the development of educational programmes for doctors in Lithuania. The policy lead in Estonia stated that no research had been conducted on support for healthcare professionals in addressing patients' non-adherence, so the extent to which this support is provided was unknown.

Partnership approach

A partnership approach between patients and healthcare professionals was reported as implicit within the health systems of three countries: Germany, Ireland and Malta. Policy leads in these countries indicated that healthcare professionals are aware of the importance of implementing a partnership approach. The interviewee for Germany commented that doctors and pharmacists may

not explicitly discuss the need for a partnership approach with patients, but are nonetheless aware of the need to use such an approach.

Interviewees representing Ireland and Malta suggested that the health system culture in their nations now served to promote a partnership approach with patients, through the transition from a more paternalistic situation to one in which patients are able to participate more actively in decisions about their medicines.

Inter-profession collaboration

Collaboration between professions in addressing patients' non-adherence was reported to varying degrees in Germany, Ireland and the Netherlands. While the policy lead in the Netherlands described an established system of collaboration between pharmacists and doctors at the state level to ensure that information provided to patients is consistent, the policy lead in Germany mentioned proposed activities for improving the co-working between pharmacists and doctors within an action plan for drug safety. This interviewee acknowledged the need to improve cooperation, not only from the perspective of drug safety but also in a more general way. The policy lead for Ireland stated that steps had been taken towards promoting a collaborative approach between healthcare professions. For instance, the Health Service in Ireland pays pharmacists a non-dispensing fee for medication prescribed but not dispensed, as an incentive to encourage collaboration between medical practitioners and pharmacists about the appropriateness of medicines.

The role of technology in adherence

Policy leads in Ireland, Lithuania, Malta and the Netherlands described the abundance of objective information about medicines on the internet, including summaries of product characteristics and patient information leaflets. However, the use of this information by patients was unknown. The interviewee for the Netherlands explained that technology was being utilised to develop a nation-wide monitor on adherence, to assess whether initiatives to increase adherence have resulted in improved use of medicines. This monitor will allow comparisons to be made between different diseases and regions. Electronic systems to collate and share information on dispensing of prescriptions were discussed by the interviewees for Estonia and Lithuania. A digital system containing patients' medicines histories is used by general practitioners to infer patients' adherence in Estonia, while an electronic prescribing system is under development in Lithuania. The policy lead in Ireland stressed the importance of health information technology in facilitating the sharing of information to deliver consistent adherence support, increasing public awareness of adherence, and enabling healthcare professionals to spend more time with patients. Such technology was described as having the potential to improve practice and produce a more cost efficient health system.

Advice for other nations

With regard to advice for other nations, cooperation between stakeholders was described as particularly important. The interviewees for Finland, Malta and the Netherlands referred to the need to engage all parties, such as patients, pharmacists, doctors and government, in the planning and

implementation of activity for adherence. Other recommendations offered by these countries included recognising adherence as a problem to be addressed, striving for national level coordination in initiating activity, and using clear treatment guidelines to facilitate standardisation. The policy lead for Malta also suggested the targeting of interventions to those areas that would result in the greatest benefit, both financially and in terms of patient outcomes.

Comprehensiveness of the policy solutions

Six interviewees were asked about the comprehensiveness of the policy solutions and all felt that they provided a complete account of the activity needed to address non-adherence. None of the interviewees suggested additional solutions.

8.6.4 Discussion

8.6.5 Main findings and conclusions

European policy leads for medicines use differ in their perceptions of the extent to which policies to support medication adherence have been implemented in their own countries. Policy leads reported that more implementation had taken place for solutions at the patient, patient-clinician interaction, and medicine levels than solutions at government or healthcare payer levels of action. In general across the 10 countries, implementation of medication adherence policy solutions was perceived to be insufficient. Medicines policy leads noted that medication adherence has limited visibility within policy documents, can be overshadowed by other health policy issues, and that difficulty demonstrating impact makes it harder to make a case for investment in adherence support. Countries with more successful implementation have a number of characteristics: co-ordinated multi-stakeholder forums, national level support and drive, and a patient-centred approach to healthcare.

8.6.6 Strengths and limitations

This is the first study we are aware of to examine the extent of implementation of medication adherence policy solutions and to do so across a number of countries. In the absence of medication adherence outcome indicators, or benchmarks for medication adherence support, key informant interviews with medicines policy leads are an effective method for exploring the factors that influence how options for medication adherence implementation are formulated and the factors that determine the nature and level of implementation. Furthermore, as the subjective beliefs and opinions of policy makers are likely to have some impact on policy decisions,[57] the ways in which policy makers perceive and understand the nature of medication adherence and the potential policy options for supporting medication adherence, are of interest.

Social desirability bias to the survey may have led respondents to report more medication adherence implementation than is actually the case, to give a favourable impression of health

service provision in their country. Several factors should be taken into account here. Firstly, all respondents were potentially exposed to social desirability bias yet varying perceptions of the level of implementation were reported. Seven of the ten respondents participated in follow-up interviews and responses to the survey were discussed in detail. Participants would likely have encountered difficulty discussing and exploring their survey responses during interview if those responses were fallacious. Also, many respondents reported that the implementation of specific policy solutions was insufficient, an unlikely response if participants were weighted by a heavy social desirability bias.

8.6.7 Implications and recommendations

The medicines policy leads described the implementation of medication adherence policy, in general, to be less than ideal and described a number of factors that impede them from formulating and implementing policy solutions in this area.

Given the multi-dimensional nature of medication adherence and the way in which responsibility for medication adherence cuts across healthcare professional groups and healthcare sectors, the low level of action reported at the systems and Government levels is a concern. Examples of action at these levels were reported by a minority of nations, for example, the use of multi-stakeholder national forums and a policy drive to address medication adherence, and serve as models for other countries struggling to implement policy solutions in this area. The need to raise the profile of medication adherence in health policy formulation, reported to be hidden or invisible in policy documentation in many countries, also emerges as a priority for the medication adherence community.

In the majority of countries surveyed, activity to enhance or support medication adherence was rarely described as coordinated or part of a larger strategic policy programme, but seemed instead to emerge in a more *ad-hoc* fashion and be focussed at interventions aimed at modifying or supporting individual patient behaviour. When activity was planned it was also often targeted. Two main targeting strategies emerged: a focus on high prevalence long-term conditions, such as diabetes and asthma, and a focus on patients prescribed medicines with an element of complexity such as a requirement for additional monitoring for safety purposes, or medicines which are known to be more problematic. The relative efficacy of these two strategies for enhancing medication adherence is unknown.

Several factors mentioned by the medicines lead hinder productive policy making in this area, and are also less amenable to rapid change. The medicines policy leads were short of evidence for the clinical and cost-effectiveness of intervening to address medication adherence, making it difficult for them to build a strong case for investment. Only one country - the Netherlands - reported that the *prima facie* evidence of the size of the problem of medication adherence and the implicit consequences of non-adherence for morbidity and mortality were sufficient in themselves to stimulate Government level action. In the medium to long term, it would seem likely that convincing

evidence of the cost and clinical benefits of medication adherence support, well communicated to policy makers, will be necessary to stimulate concerted action to address medication adherence. Taken together with the conclusions of Chapter 7, notably the distinct lack of evidence concerning cost-effectiveness of adherence interventions over the last 30 years, the ABC Project team have a strong case for recommending that activity to support the production of cost-effectiveness evidence is a key priority for future action.

This study demonstrates that while European countries differ in some key ways, such as the extent to which patient-centred care is dominant in healthcare culture, medicines policy leads experienced similar difficulties and challenges in implementing medication adherence policy solutions, and shared similarities in the nature of successful implementation. This suggests that co-ordinated action between countries at European level and the sharing of good practice in medication adherence policy formulation and policy implementation may be beneficial.

8.7 Research-based recommendations for medication adherence for Europe

8.7.1 Introduction

Research undertaken for the ABC Project, described in previous chapters, has resulted in a number of recommendations and priorities for future action for European nations, to address medication adherence, optimise medicines use, and support the clinical and cost-effective use of medicines. The recommendations from each chapter have been collated here and are presented with the consensus-based recommendations described earlier in this chapter. The consensus-based recommendations had been the focus of a consensus meeting in June 2011. The research-based recommendations were presented and discussed at another meeting organised by the ABC Project: the European Forum on Patient Adherence to Medication in December 2011 at the European Parliament Building.

8.7.2 Method

The research outcomes from each work package within the ABC Project were examined by the research study authors to consider whether implications for policy could be extrapolated to form research-based recommendations for Europe. Draft recommendations from each work package were developed and circulated to the ABC Project team for discussion and refinement.

The draft research-based recommendations were presented and discussed at the ‘European Forum on Patient Adherence to Medication’ an ABC Project hosted event. The research-based recommendations were subsequently reviewed again by study leads, and edited to incorporate any learnings from the forum. Revised recommendations were then circulated to ABC Project team members.

8.7.3 Results

Draft research-based recommendations, presented at the European Forum on Patient Adherence to Medication are shown in the table below.

Table 8.5 Research-based recommendations presented at the European Forum on Patient Adherence to Medication

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Definitions of adherence:

- Any initiatives in respect to patient adherence to medications should address its 3 distinct elements:
  - initiation – implementation – discontinuation
- Management of adherence derives benefit from a 'system-based' approach, wherein each stakeholder has a specific role to play:
  - the patient, their family & relatives, healthcare providers, institutions, and healthcare systems

Determinants, causes and models of medication adherence:

- Key targets
  - improvement in self-efficacy
  - reducing barriers to medication
- Determinants of adherence differ by country (and by the outcome measures used)
- Management of adherence in patients co-prescribed multiple medicines for chronic and acute conditions may require different approaches
- Patients' preferences for drug attributes influence their decision to continue taking a medicine and should be considered when developing new medicines, formulations or interventions
- Assessment of the theoretical basis of adherence behaviour should inform the development of adherence enhancing interventions
- Consolidation of behavioural models across disciplines will benefit the development of interventions that promote a more sustainable behaviour change

Healthcare professionals:

- Educational framework with 3 components:
  - Competency framework
  - Curriculum
  - Diagnostic tool for assessing competence
- Adherence should be included in curricula for all healthcare professionals, especially doctors, nurses, and pharmacists
- Specific, evidence-based practice guidelines are needed

Adherence interventions:

- Interventions intended to manage adherence should include, beside education, motivation and performance-based feedback to achieve measurable, pharmacologically sound goals

- The effects of interventions wane over time, calling for innovative approaches to achieve sustainable management, validated by long-term program evaluation
- More quality evidence on the cost-effectiveness of adherence-enhancing interventions is necessary

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The European Forum on Patient Adherence to Medication was granted the patronage of the European Parliament, the Polish Presidency of the Council of the European Union and Jacek Saryusz-Wolski, MEP. Nearly 100 participants took part in the conference, with European policymakers, academics, insurance companies' representatives, health professionals, patients' organizations representatives, journalists and other stakeholders among them.

The draft research-based recommendations were discussed and finalised subsequent to the meeting and the research-based and consensus-based recommendations were combined and discussed. The ABC medication adherence policy recommendations are presented below in Table 8.6.

Table 8.6 ABC medication adherence policy recommendations for Europe

Overview

Policy formulation and implementation for medication adherence:

- derives benefit from a system-based approach, which recognises the role of all medication adherence stakeholders: the patient, their family & carers, healthcare providers and payers, healthcare professionals, educators and researchers and the pharmaceutical industry
- should consider the drug and disease characteristics, patients' overall health status, and the relative importance of the drug in the patient's overall care
- should include interventions that target the three components of medication adherence: initiation, implementation, and persistence with medication taking
- should take behavioural theories into account, to further our understanding of factors that influence medication adherence and actions that can best improve adherence
- should be sensitive to patient 's beliefs and preferences
- should include interventions that are supported by evidence on clinical effectiveness and which result in clinically- and cost-effective medications when taken according to the label instructions.

Patients and carers

- Interventions to manage adherence to medications should include, as a minimum, education and information for patients to increase their knowledge about the disease and treatment. When appropriate, motivation and performance-based feedback of medication taking should also be provided.
- Interventions to manage medication adherence should be prioritised when:
  - a medication is newly prescribed
  - a change in treatment or dosing regimen is considered
  - several medications are prescribed
  - agreed treatment goals are not achieved
  - adverse drug reactions are anticipated or experienced
  - when the patient requests assistance with medication taking.

Healthcare professionals

- Healthcare professional education should include theoretical and practical training in managing medication adherence, as described in the ABC Project *A framework for the education and training of health professionals in Europe.*
- Healthcare professionals should receive education and training in order to identify non-adherence, and optimise medication adherence.

Clinician-patient interaction

- A collaborative approach between patients and healthcare professionals should be adopted to facilitate optimal medicines use and patient-centred care.
- Together, healthcare professionals and patients should:
  - discuss the patients' preferences for treatment
  - ensure a partnership approach in decision making and treatment
  - discuss the patients' health and medication-related beliefs
  - build the patients' trust in the healthcare professional.

Healthcare teams/providers

- Healthcare providers should:
  - promote a team approach, sharing information to deliver consistent adherence support
  - prioritise medication adherence support in service, organisation, and systems design.

Governments/healthcare payers

- Governments/healthcare payers should
  - increase public awareness of medication adherence for all citizens
  - recognise the importance of cost to patients as a barrier to adherence
  - develop and implement evidence-based interventions for medication adherence
  - provide undergraduate and postgraduate training and guidance for all healthcare providers so they can deliver effective adherence interventions
  - invest in research to identify effective interventions demonstrating value for money, such that
    - more quality evidence accumulates on the cost-effectiveness of adherence-enhancing interventions
    - the theoretical basis of adherence behaviour informs the development of adherence enhancing interventions
    - improved approaches are developed to achieve sustainable adherence management.

8.7.4 Discussion

8.7.5 Main findings and conclusions

The ABC Project has produced policy recommendations for Europe concerning medication adherence. The recommendations, based on research with a variety of methodologies, cover a range of targets of action, including interventions and actions to assist patients with medicines use, for healthcare professionals in their clinical practice, for those involved in the design and provision of adherence-focussed interventions and those involved in medication adherence policy formulation and implementation.

8.7.6 Strengths and limitations

Research on the causes, consequences and interventions to address medication non-adherence, including the research described in this report, can potentially inform the policy response to medication non-adherence. In practice, the adoption and implementation of research-based evidence, even when the research is of good quality, can be complicated. Macintyre and colleagues[58] describe a number of ways in which research evidence can be limited in usefulness to policymakers. For example, some well-intentioned research-based policy recommendations (sleeping position for newborns; prescription of bed rest) have been found to cause harm rather than provide benefit and have achieved the opposite outcome to that intended.[58] Further, the evidence base is rarely 'complete'. Moreover, there can be differences in the quality and quantity of research evidence at different levels of action:

> "The evidence for the effectiveness of suggested interventions was usually clearer for more specific, 'downstream' proposals that focused on individuals (for example, smoking cessation strategies such as nicotine replacement therapy) than for more macro level, 'upstream' proposals focusing on legislation or cost (for example, using fiscal policies to affect smoking prevalence)….The fact that there is more evidence available about interventions aimed at individuals does not mean that interventions aimed at whole communities are not effective but rather reflects the paucity of good quality studies of these more 'upstream' interventions" (Macintyre and colleagues[58], p. 322).

For some types of interventions, Macintyre and colleagues[58] cite fiscal measures to modify smoking and alcohol consumption as examples, randomised experimental evidence will never be available, and so available to inform policy decisions. Thus even when research evidence is available and can be used to inform policy decisions, that evidence may be incomplete, cover only some forms of policy response, and may not translate into positive outcomes for patients and the public.

In addition to these general observations about the ways and extent to which research evidence can inform health policy, there are a number of specific factors in the medication adherence field that mitigate against a strong uptake of research evidence by policymakers. The research presented in this report goes some way towards addressing this.

Research with public policymakers demonstrates that they appreciate brevity and clear, simple messages, rather than academic-oriented publications to inform their views and actions.[4] As described in Chapter 2, a number of terms, and concepts underpinning those terms, have been used in the medication adherence field. Multiple terms for similar concepts, and misuse of those terms, may hinder the non-specialist policymaker from engaging with the adherence field and its' literature. The taxonomy presented in Chapter 2 is intended to add clarity to the terminology used in the field. In Chapter 4 we saw also that a range of theoretical and conceptual models have previously been used to explain the causes of non-adherence. Theoretical plurality benefits a burgeoning and growing research literature as common causes of non-adherence across a range of illnesses and medications are found and exceptions to the rule are identified. However, the hard-pressed policymaker may find diversity in the medication adherence narrative a barrier to action: how can we fix the problem of non-adherence if the experts can't agree on what it is and what causes it?

A specific focus of medication adherence research has been the individual beliefs and behaviours associated with variation in medicine taking behaviour, like that reported in Chapter 3. The majority of interventions to support medication non-adherence have, in turn, been based on attempts to influence, alter and change the beliefs and behaviour of people prescribed medicines (see Chapter 6 of this report). In comparison, relatively little is known about the ways in which routine clinical practice by healthcare professionals supports or hinders patients with medicines. Chapter 5 has added to our understanding of healthcare professional behaviour and showed us that in day to day practice, healthcare professionals undertake few interventions to support patients with medication taking, display a cognitive bias that their own patients have more effective medication taking than average, and report barriers to supporting medication taking, in particular access to training.

Research presented in earlier chapters of this report, and used to inform the policy recommendations in this chapter, thus addresses some of the deficits in knowledge, evidence and theory about medication adherence which could impede the uptake of research evidence by policymakers.

This chapter describes a range of potential policy responses intended to support patients with medicines taking, optimise medicines use and ensure clinical and cost-effective use of medicines. A range of methodologies are used in this chapter, to harness stakeholder opinion and input to inform policy solutions and educational initiatives, to study key informants involved in medicines policy to better understand the policy making and implementation process relevant to medication adherence,

and to disseminate the knowledge, evidence and learnings from the ABC Project to the wider healthcare community of patients, clinicians, providers, payers, educators, industry and academics.

However, to secure the uptake of ABC policy recommendations by European nations, and to further support medication adherence stakeholders to apply research learnings for the benefit of patients and the public, will take further concerted action beyond the scope of the ABC Project. This chapter does however point to future actions and research needed to support this goal.

The medication adherence research field enjoys a multi-disciplinary, multi-profession approach in which a variety of disciplines, approaches, and evidence are utilised to understand this multi-faceted problem. Transdisciplinarity may lead to a more complete, full understanding of medication adherence. However, without 'ownership' and championing of the importance of medication adherence to public health by researchers and other stakeholders, the medication adherence message may be diluted and fail to reach policy makers.

The consensus meeting and dissemination event provided a unique opportunity for interested parties in medication adherence to come together and share perspectives. A number of existing forums currently exist to support medication adherence shared learning, but these tend to be organised for the benefit of specific sectors (such as, ESPACOMP for academics; EyeforPharma patient communication and adherence conference for the pharmaceutical industry; forums organised by the Pharmaceutical Group of the European Union (PGEU). The sharing and exchange of perspectives and experiences across sectors, professions, and nations, with the involvement of patient groups, will continue to be essential for the effective development of responses to this multi-faceted issue.

The self-assessment study used medicines policy leads from a number of countries as key informants to understand the selection, implementation, and barriers to implementation, of policies addressing medication adherence. While a broad brush survey of a number of countries can provide a high-level impression of activity, a more detailed understanding of policy formulation and implementation requires studies looking in greater depth, rather than reliance on individual informants.

Whilst we have some information about the operational and political feasibility of some of the policy options available, more information is needed about prioritisation and implementation of policy options in individual countries which differ in the sophistication of their healthcare provision, culture of patient-centred care and health literacy and involvement of the population. For example, we present clear evidence in Chapter 6, and a related policy recommendation in Table 8.6, that providing feedback to patients about their medicine taking, and targeted support on the basis of that feedback, results in enhanced medication adherence. European countries vary in their readiness to implement sophisticated medication adherence interventions like this within their healthcare systems and vary in their political, policy and financial readiness to do so. At present, we need more

evidence of the precursors that need to be in place within healthcare services and health cultures to support the successful implementation of such interventions. Furthermore, we need cost-effectiveness information and systems level knowledge to enable policymakers to formulate and subsequently implement policy solutions such as this one.

8.7.7 Implications and recommendations

Non-adherence to prescribed medication can have a deleterious effect on patients' health and well-being, in addition to a serious economic impact. The World Health Organisation[26] has estimated that 30 to 50 percent of medications are not taken as prescribed, describing non-adherence as "a worldwide problem of striking magnitude". The widespread incidence of non-adherence indicates the need for policies to ensure safer, effective, and cost-effective use of medication in Europe and elsewhere. The 'Ascertaining Barriers to Compliance' (ABC) project goes some way towards addressing this need, setting out policy recommendations that can be the basis for further discussion and policy formulation within European nations.

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Appendices

Appendix 2.1 Definitions of adherence: specific search combinations used in each database

1. MEDLINE via Pubmed

(‘Patient compliance’[Majr] OR ‘Treatment Refusal’[Majr]) AND [‘Classification ‘[Subheading] OR ‘Terminology as Topic’[MeSH] OR ‘Concept Formation’[MeSH] OR ‘Vocabulary, Controlled’[MeSH] OR ‘primary adherence’[All Fields] OR ‘primary non-adherence’[All Fields] OR ‘readiness’[All Fields] OR ‘pharmionics’[All Fields] OR ‘treatment acceptance’[All Fields] OR ‘concordance’[All Fields] OR ‘definition’[All Fields] OR ‘taxonomy’[All Fields] OR ‘terminology’[All Fields] OR ‘persistence’[All Fields] OR ‘medication possession ratio’[All Fields] OR ‘meta-analysis’[All Fields])

2. EMBASE

('Patient compliance/exp/mj) AND ['Primary compliance OR 'Primary non-compliance’ OR 'Readiness' OR 'Pharmionics' OR 'Treatment acceptance' OR 'Concordance' OR 'Persistence' OR 'Meta-analysis'/exp OR 'Definition' OR 'Taxonomy'/exp OR 'Terminology'/exp OR 'Concept') AND [EMBASE]/lim

3. CINAHL

(‘ Adherence ’ OR ‘ Compliance ’ OR ‘ Persistence ’ OR ‘ Concordance ’ OR ‘ Nonadherence ’ OR ‘ Non-adherence ’ OR ‘Noncompliance ’ OR ‘ Non-compliance ’) AND (‘Terminology’ OR ‘Classification’ OR ‘Taxonomy’ OR ‘Definition’)

4. The Cochrane Library

(‘Patient compliance’ [MeSH term] AND [‘Primary compliance’[topic] OR ‘Primary non-compliance’ [topic] OR ‘Readiness’ [topic] OR ‘Pharmionics’ [topic] OR ‘Treatment acceptance’[topic] OR ‘Meta-analysis’ [topic] OR ‘Concordance’ [topic] OR ‘Definition’ [topic] OR ‘Taxonomy’ [topic] OR ‘Concept’ [topic] OR ‘Persistence’ [topic] OR ‘Medication possession ratio’ [topic])

5. PsycINFO

(‘Compliance’ OR ‘Adherence’ OR ‘Concordance’ OR ‘Persistence’ OR ‘Noncompliance’ OR ‘Non-Compliance’ OR ‘Nonadherence’ OR ‘Non-adherence’) AND (‘Classification’ OR ‘Taxonomy’ OR ‘Definition’ OR ‘Terminology’)

Appendix 3.1 Determinants of patient adherence systematic review: search strategy used in MEDLINE (via Pubmed) database

1. patient compliance [majr]
2. patient dropouts [majr]
3. treatment refusal [majr]
4. directly observed therapy [majr]
5. medication adherence [majr]
6. concordance [tiab] AND patient compliance [mh]
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
8. factor [tw] OR factors [tw]
9. variable [tw] OR variables [tw] OR variable* [tw]
10. predictor [tw] OR predictors [tw] OR predict* [tw]
11. determinant [tw] OR determinants [tw] OR determin* [tw]
12. association [tw] OR associations [tw] OR associat* [tw]
13. 8 OR 9 OR 10 OR 11 OR 12
14. 7 AND 13
15. systematic [tw]
16. 14 AND 15
17. 14 Limits: Systematic Reviews
18. 16 OR 17
19. Limits: Publication date from 2000/01/01 to 2009/12/31
20. Limits: Humans, English

Appendix 3.2 Determinants of patient adherence systematic review: study characteristics and results

I: implementation
P: persistence
NS: not stated

References	Field	Patient group	Databases searched	Study design	Adherence component	Treatment duration	Positive effect on adherence					Negative effect on adherence				
							Patient-related factors	Condition-related factors	Therapy-related factors	Socio/economic-related factors	HCT-related factors	Patient-related factors	Condition-related factors	Therapy-related factors	Socio/economic-related factors	HCT-related factors
Bao et al. 2009[3]	opioid dependance	NS	CMKI, EMBASE, MEDLINE	meta-analysis	P	long-term			+							
Bramlage et al. 2009[4]	hypertension	NS	PubMed	systematic review	P	long-term			+							
Brandes et al. 2009[5]	multiple sclerosis	NS	CINAHL, IPA, MEDLINE	systematic review	NS	long-term	+	+				+		+		
Broekmans et al. 2009[6]	non-malignant chronic pain	adults	Cochrane, CINAHL, MEDLINE, PsycINF	systematic review	I	long-term						+	+	+		+
Charach et al. 2008[7]	ADHD	children	CINAHL, EMBASE, MEDLINE, PsycINFO	systematic review	P	long-term	+	+	+		+	+		+	+	+
Chia et al. 2006[8]	general	elderly	Academic Search Primer, Adis, Anthropology Plus, Cumulative Index to Allied Health Literature, Ethnic Newswatch, IPA, EMBASE, MEDLINE, PsycINFO,	systematic review	I	long-term	+	+	+		+	+				

References	Field	Patient group	Databases searched	Study design	Adherence component	Treatment duration	Positive effect on adherence					Negative effect on adherence				
							Patient-related factors	Condition-related factors	Therapy-related factors	Socio/economic-related factors	HCT-related factors	Patient-related factors	Condition-related factors	Therapy-related factors	Socio/economic-related factors	HCT-related factors
			Sociological Abstracts													
Claxton et al. 2001[9]	general	NS	Cochrane, Health & Psychosocial Instruments, HealthStar, MEDLINE, PsycINFO	systematic review	I	long-term								+		
Connor et al. 2004 [10]	general	adults	CINAHL, Cochrane, EMBASE, IPA, MEDLINE, metaRegister of Controlled Trials	systematic review	I	long-term			+							
Costello et al. 2008[11]	multiple sclerosis	NS	MEDLINE	systematic review	I	long-term	+		+	+		+	+	+	+	+
Cramer et al. 2004[12]	diabetes	NS	Cochrane, Current Contents, Health & Psychosocial Instruments, MEDLINE	systematic review	I	long-term	+	+					+			
DiMatteo et al. 2007[13]	general	children, adults	old MEDLINE, PsychLit, PubMed	meta-analysis	I + P	long-term	+				+					
DiMatteo et al. 2000[14]	general	children, adults	MEDLINE, PsychLit	meta-analysis	I	long-term						+				
DiMatteo et al. 2004[15]	general	children, adults	MEDLINE, PsychLit	meta-analysis	I	long-term				+					+	
DiMatteo et	general	children, adults	Index Medicus, MEDLINE,	meta-analysis	I	long-term	+	+					+			

References	Field	Patient group	Databases searched	Study design	Adherence component	Treatment duration	Positive effect on adherence					Negative effect on adherence				
							Patient-related factors	Condition-related factors	Therapy-related factors	Socio/economic-related factors	HCT-related factors	Patient-related factors	Condition-related factors	Therapy-related factors	Socio/economic-related factors	HCT-related factors
al. 2004[16]			PsychLit													
Fogarty et al. 2002[17]	HIV	NS	Cochrane, PsycINFO, MEDLINE, Sociofile	systematic review	P	long-term	+				+	+		+	+	
Gold et al. 2006[18]	osteoporosis	NS	MEDLINE	systematic review	P	long-term	+				+		+	+	+	
Gonzalez et al. 2008[19]	diabetes	children, adults	MEDLINE, PsycINFO	meta-analysis	NS	long-term						+				
Hirsch-Moverman et al. 2008[20]	tuberculosis	adults	MEDLINE, PsycINFO, PubMed	systematic review	I	long-term	+	+	+	+		+	+			
Hodari et al. 2006[21]	dermatological diseases	NS	PubMed	systematic review	I	long-term	+					+	+	+		+
Iskedjian et al. 2002[22]	hypertension	adults	EMBASE, MEDLINE, IPA	meta-analysis	I	long-term			+							
Jacobsen et al. 2009[23]	cancer	adults	Cochrane, EMBASE, MEDLINE, Web of Science	systematic review	I	long-term					+	+				
Jindal et al. 2003[24]	post kidney transplant patients	NS	MEDLINE	systematic review	I	long-term	+					+	+			
Julius et al. 2009[25]	psychiatric disorders	NS	Ovid, Medline	systematic review	I	long-term	+			+	+	+		+	+	+

References	Field	Patient group	Databases searched	Study design	Adherence component	Treatment duration	Positive effect on adherence					Negative effect on adherence				
							Patient-related factors	Condition-related factors	Therapy-related factors	Socio/economic-related factors	HCT-related factors	Patient-related factors	Condition-related factors	Therapy-related factors	Socio/economic-related factors	HCT-related factors
Kahana et al. 2008[26]	post transplant patients	children	Psyc-INFO, PUBMED/MEDLINE	systematic review	I	long-term						+		+	+	
Karamanidou et al. 2008[27]	end stage renal disease	adults	CINAHL, EMBASE, PsycINFO, MEDLINE	systematic review	I	long-term	+			+		+			+	
Kruk et al. 2006[28]	general	NS	IPA, MEDLINE	systematic review	I	long-term			+							
Lacro et al. 2002[29]	schizofrenia	NS	HealthSTAR, MEDLINE, PsycINFO	systematic review	I	long-term						+	+	+		+
Lanouette et al. 2009[30]	psychiatric disorders	adults (US Latinos)	M EDLINE, PsycINFO	systematic review	I + P	long-term	+	+	+	+		+				+
Lee et al. 2006[31]	diabetes	NS	MEDLINE, Pubmed	systematic review	I + P	long-term			+						+	
Lewiecki et al. 2007[32]	osteoporosis	adults	Cochrane, MEDLINE	systematic review	I	long-term		+				+		+		
Lovejoy et al. 2009[33]	HIV	HIV-positive adults	MEDLINE, PsycINFO	systematic review	I	long-term						+				
Malta et al. 2008[34]	HIV	HIV-positive drug users	AIDSLINE, AMED, CINAHL, Cochrane, MEDLINE, TOXNET, Web of Science	systematic review	I + P	long-term					+	+		+		
Mills et al.	HIV	NS	AMED, Campbell Collaboration	systematic review	NS	long-term	+		+	+	+	+		+	+	+

References	Field	Patient group	Databases searched	Study design	Adherence component	Treatment duration	Positive effect on adherence					Negative effect on adherence				
							Patient-related factors	Condition-related factors	Therapy-related factors	Socio/economic-related factors	HCT-related factors	Patient-related factors	Condition-related factors	Therapy-related factors	Socio/economic-related factors	HCT-related factors
2006[35]			Cochrane, CINAHL, EMBASE, ERIC, MEDLINE, NHS EED													
Munro et al. 2007[36]	tuberculosis	NS	Academic Search Premier, CINAHL, EMBASE, ERIC, MEDLINE, Pre-CINAHL, PapersFirst, PsycINFO, PubMed, dissertation abstracts, sociological abstracts, social services abstracts, PAIS international, Health Source: Nursing/Academic, ScienceDirect, Social Science full text, Social science citation expanded, social science citation index, arts and humanities citation index	systematic review	I + P	long-term	+	+	+	+	+	+	+	+	+	+
Nosé et al. 2003[37]	psychosis	NS	MEDLINE, PsycINFO	systematic review	I	long-term	+	+		+	+	+	+	+	+	

References	Field	Patient group	Databases searched	Study design	Adherence component	Treatment duration	Positive effect on adherence					Negative effect on adherence				
							Patient-related factors	Condition-related factors	Therapy-related factors	Socio/economic-related factors	HCT-related factors	Patient-related factors	Condition-related factors	Therapy-related factors	Socio/economic-related factors	HCT-related factors
Oehl et al. 2000[38]	psychosis	NS	MEDLINE	systematic review	NS	long-term	+		+	+		+	+	+	+	+
Olthoff et al. 2005[39]	glaucoma	NS	CINAHL, Cochrane MEDLINE, EMBASE, PsycINFO	systematic review	I + P	long-term	+	+			+	+		+		+
Pampallona et al. 2002[40]	depression	NS	Cochrane, Current Contents, MEDLINE, PsycInfo	systematic review	I	long-term						+	+	+		+
Parienti et al. 2009[41]	HIV	NS	PubMed, recent HIV science conferences	meta-analysis	I	long-term			+							
Ramos et al. 2009[42]	HIV	children	MEDLINE, EMBASE, conference abstract	systematic review	NS	long-term			+							
Reisner et al. 2009[43]	HIV	youth (13-24 years)	PubMed, PsycINFO, MEDLINE	systematic review	I + P	long-term	+	+	+	+	+	+	+	+	+	
Ruddy et al. 2009[44]	cancer	children	PubMed	systematic review	I + P	long-term	+	+			+	+	+	+	+	
Santarlasci et al. 2003[45]	schizophrenia	NS	MEDLINE	systematic review	P	long-term								+		
Schmid et al. 2009[46]	end stage renal disease	adults	PubMed, Medline	systematic review	NS	long-term	+		+			+	+		+	+
Van Der Wal et al.	heart failure	adults	CINAHL, MEDLINE	systematic review	I	long-term	+	+	+		+			+		

References	Field	Patient group	Databases searched	Study design	Adherence component	Treatment duration	Positive effect on adherence					Negative effect on adherence				
							Patient-related factors	Condition-related factors	Therapy-related factors	Socio/economic-related factors	HCT-related factors	Patient-related factors	Condition-related factors	Therapy-related factors	Socio/economic-related factors	HCT-related factors
2005[47]																
Vermeire E et al. 2001[48]	general	NS	EMBASE, ERIC, PsycINFO, MEDLINE, Sociological abstracts, Dissertation abstracts	systematic review	I	long-term	+	+		+	+	+	+	+		+
Vik et al. 2004[49]	general	elderly	IPA, MEDLINE, PubMed,	systematic review	I	long-term					+	+		+		+
Vreeman et al. 2008[50]	HIV	children	EMBASE, MEDLINE, relevant websites	systematic review	I	long-term	+					+		+	+	
Weiner et al. 2008[51]	cystic fibrosis	children, adults	MEDLINE, selected conference abstracts	systematic review	I	long-term	+		+		+	+		+	+	
Wetzels et al. 2004[52]	hypertension	NS	MEDLINE, PubMed, EMBASE	systematic review	I	long-term			+					+		
Yeung et al. 2005[53]	malaria	children, adults	EMBASE, PubMed, web sites	systematic review	I	long-term			+							

Appendix 3.3 Discrete choice experiment: levels for 'potentially life-threatening ADR' by country and language

Country	Language	Section 4.8 Undesirable effects Adverse reactions reported are listed according to the following frequency:		
		1/100	**1/1,000**	**1/10,000**
Austria	German	Gelegentlich	Selten	Sehr selten
Belgium	French	Peu fréquents	Rares	Très rares
Belgium	Dutch	Soms	Zelden	Zeer zelden
England	English	Uncommon	Rare	very rare
France**	French	Peu fréquents	Rares	Très rares
Germany	German	Gelegentlich	Selten	Sehr selten
Greece	Greek	Όχι συχνές	Σπάνιες	Πολύ σπάνιες
Hungary	Hungarian	Nem gyakori	Ritka	Nagyon ritka
Netherlands	Dutch	Soms	Zelden	Zeer zelden
Poland	Polish	Niezbyt często	Rzadko	Bardzo rzadko
Portugal**	Portuguese	Pouco frequentes	Raras	Muito raras
Wales (UK)	English	Uncommon	Rare	very rare
Wales (UK)	Welsh*	Anghyffredin	Anaml	Prin iawn

***Country not included in analysis as did not meet required sample size of n>100 ;*
**Forward and back translation from English version*

** EMA: Product Information: Section 4.8 :*
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000710/human_med_000796.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125&jsenabled=true

Appendix 3.4 Discrete choice experiment: results by adherence subgroups

Table A3.1
Unrestricted random-effects logit regression model for Austria: *Adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.034	0.006	0.000	0.023	0.045		-2.24
Dose OD						31.37	-70.17
_BD	-0.362	0.079	0.000	-0.517	-0.207	-10.58	23.67
_QDS	-0.711	0.083	0.000	-0.874	-0.549	-20.79	46.50
Mild ADR	-0.015	0.002	0.000	-0.019	-0.012	-0.45	
Severe ADR						14.22	-100.10
_rare	-0.471	0.077	0.000	-0.622	-0.321	-13.77	30.80
_uncommon	-1.060	0.072	0.000	-1.202	-0.918	-30.98	69.30
_cons	0.461	0.079	0.000	0.306	0.615		
No. of obs =	1878						
No. of groups =	212						
Wald chi^2 (6) =	311.030						
Log likelihood =	-1038.168						

Table A3.2
Unrestricted random-effects logit regression model for Austria: *Non-adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.034	0.009	0.000	0.017	0.052		-2.28
Dose OD						38.20	-86.94
_BD	-0.520	0.121	0.000	-0.757	-0.284	-15.12	34.42
_QDS	-0.794	0.130	0.000	-1.050	-0.538	-23.08	52.52
Mild ADR	-0.015	0.003	0.000	-0.020	-0.010	-0.44	
Severe ADR						15.61	-136.37
_rare	-0.522	0.112	0.000	-0.742	-0.302	-15.17	34.53
_uncommon	-1.540	0.123	0.000	-1.780	-1.299	-44.75	101.84
_cons	0.608	0.092	0.000	0.428	0.787		
No. of obs =	969						
No. of groups =	109						
Wald chi^2 (6) =	183.090						
Log likelihood =	-474.181						

Table A6.3
Unrestricted random-effects logit regression model for Belgium: *Adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.037	0.008	0.000	0.021	0.053		-1.36
Dose OD						11.76	-16.05
_BD	-0.213	0.116	0.066	-0.440	0.014	-5.74	7.84
_QDS	-0.223	0.119	0.061	-0.457	0.010	-6.02	8.21
Mild ADR	-0.027	0.003	0.000	-0.033	-0.022	-0.73	
Severe ADR						16.14	-65.48
_rare	-0.571	0.114	0.000	-0.795	-0.347	-15.41	21.03
_uncommon	-1.207	0.101	0.000	-1.404	-1.010	-32.58	44.45
_cons	0.488	0.100	0.000	0.293	0.683		
No. of obs =	954						
No. of groups =	109						
Wald chi^2 (6) =	209.750						
Log likelihood =	-496.549						

Table A6.4
Unrestricted random-effects logit regression model for Belgium: *Non-adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.066	0.013	0.000	0.042	0.091		-2.38
Dose OD						14.87	-35.44
_BD	-0.383	0.152	0.012	-0.680	-0.086	-5.79	13.81
_QDS	-0.600	0.179	0.001	-0.952	-0.248	-9.08	21.63
Mild ADR	-0.028	0.004	0.000	-0.035	-0.021	-0.42	
Severe ADR						8.02	-71.32
_rare	-0.502	0.149	0.001	-0.794	-0.211	-7.60	18.11
_uncommon	-1.476	0.159	0.000	-1.787	-1.165	-22.32	53.21
_cons	0.378	0.114	0.001	0.155	0.600		
No. of obs =	586						
No. of groups =	66						
Wald chi^2 (6) =	150.740						
Log likelihood =	-273.139						

Table A6.5
Unrestricted random-effects logit regression model for England: *Adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.052	0.006	0.000	0.040	0.064		-2.01
Dose OD						12.39	-24.95
_BD	-0.218	0.083	0.009	-0.381	-0.055	-4.20	8.46
_QDS	-0.425	0.089	0.000	-0.599	-0.252	-8.19	16.49
Mild ADR	-0.026	0.002	0.000	-0.030	-0.022	-0.50	
Severe ADR						5.29	-43.27
_rare	-0.249	0.083	0.003	-0.411	-0.087	-4.80	9.66
_uncommon	-0.867	0.073	0.000	-1.009	-0.725	-16.69	33.61
_cons	0.312	0.071	0.000	0.172	0.451		
No. of obs =	1583						
No. of groups =	185						
Wald chi^2 (6) =	308.190						
Log likelihood =	-869.336						

Table A6.6
Unrestricted random-effects logit regression model for England: *Non-adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.039	0.008	0.000	0.024	0.054		-1.22
Dose OD						29.46	-36.07
_BD	-0.465	0.108	0.000	-0.677	-0.252	-11.80	14.45
_QDS	-0.695	0.112	0.000	-0.914	-0.477	-17.66	21.62
Mild ADR	-0.032	0.003	0.000	-0.037	-0.027	-0.82	
Severe ADR						10.89	-46.38
_rare	-0.397	0.103	0.000	-0.598	-0.195	-10.07	12.33
_uncommon	-1.095	0.094	0.000	-1.280	-0.910	-27.80	34.05
_cons	0.344	0.082	0.000	0.184	0.505		
No. of obs =	1133						
No. of groups =	130						
Wald chi^2 (6) =	273.990						
Log likelihood =	-561.547						

Table A6.7
Unrestricted random-effects logit regression model for Germany: *Adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.021	0.007	0.002	0.008	0.034		-0.87
Dose OD						39.27	-34.36
_BD	-0.309	0.096	0.001	-0.498	-0.120	-15.02	13.14
_QDS	-0.499	0.097	0.000	-0.690	-0.308	-24.25	21.22
Mild ADR	-0.024	0.002	0.000	-0.028	-0.019	-1.14	
Severe ADR						37.57	-95.35
_rare	-0.749	0.090	0.000	-0.926	-0.572	-36.43	31.87
_uncommon	-1.492	0.088	0.000	-1.665	-1.320	-72.56	63.48
_cons	0.534	0.069	0.000	0.398	0.670		
No. of obs =	1558						
No. of groups =	179						
Wald chi^2 (6) =	358.500						
Log likelihood =	-755.404						

Table A6.8
Unrestricted random-effects logit regression model for Germany: *Non-adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.032	0.010	0.002	0.011	0.052		-1.05
Dose OD						18.32	-19.26
_BD	-0.220	0.144	0.125	-0.502	0.061	-6.98	7.34
_QDS	-0.358	0.145	0.013	-0.642	-0.074	-11.34	11.92
Mild ADR	-0.030	0.003	0.000	-0.036	-0.024	-0.95	
Severe ADR						19.19	-70.14
_rare	-0.576	0.133	0.000	-0.836	-0.316	-18.24	19.18
_uncommon	-1.530	0.123	0.000	-1.770	-1.290	-48.46	50.96
_cons	0.625	0.101	0.000	0.427	0.824		
No. of obs =	764						
No. of groups =	87						
Wald chi^2 (6) =	205.660						
Log likelihood =	-353.163						

Table A6.9
Unrestricted random-effects logit regression model for Greece: *Adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	-0.001	0.007	0.841	-0.015	0.012		0.06
Dose OD						-663.81	-38.80
_BD	-0.184	0.104	0.077	-0.388	0.020	129.63	7.58
_QDS	-0.759	0.098	0.000	-0.950	-0.568	534.18	31.22
Mild ADR	-0.024	0.002	0.000	-0.029	-0.020	17.11	
Severe ADR						-192.43	-59.05
_rare	-0.249	0.092	0.007	-0.429	-0.069	175.32	10.25
_uncommon	-1.186	0.085	0.000	-1.353	-1.019	834.87	48.80
_cons	0.586	0.072	0.000	0.445	0.727		
No. of obs =	1290						
No. of groups =	144						
Wald chi^2 (6) =	285.220						
Log likelihood =	-656.896						

Table A6.10
Unrestricted random-effects logit regression model for Greece: *Non-adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	-0.004	0.007	0.578	-0.017	0.009		0.15
Dose OD						-294.18	-43.19
_BD	-0.258	0.103	0.012	-0.459	-0.057	69.44	10.20
_QDS	-0.834	0.093	0.000	-1.017	-0.651	224.74	33.00
Mild ADR	-0.025	0.002	0.000	-0.030	-0.021	6.81	
Severe ADR						-63.90	-43.65
_rare	-0.212	0.092	0.021	-0.391	-0.032	57.09	8.38
_uncommon	-0.891	0.078	0.000	-1.044	-0.739	240.21	35.27
_cons	0.632	0.072	0.000	0.492	0.773		
No. of obs =	1268						
No. of groups =	144						
Wald chi^2 (6) =	275.030						
Log likelihood =	-668.335						

Table A6.11
Unrestricted random-effects logit regression model for Hungary : *Adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.039	0.008	0.000	0.022	0.055		-2.38
Dose OD						20.46	-48.67
_BD	-0.192	0.117	0.100	-0.420	0.037	-4.92	11.71
_QDS	-0.604	0.124	0.000	-0.847	-0.362	-15.54	36.96
Mild ADR	-0.016	0.003	0.000	-0.022	-0.011	-0.42	
Severe ADR						13.64	-100.50
_rare	-0.514	0.114	0.000	-0.739	-0.290	-13.22	31.44
_uncommon	-1.129	0.108	0.000	-1.341	-0.918	-29.03	69.06
_cons	0.514	0.110	0.000	0.298	0.731		
No. of obs =	858						
No. of groups =	96						
Wald chi^2 (6) =	147.900						
Log likelihood =	-466.884						

Table A6.12
Unrestricted random-effects logit regression model for Hungary : *Non-adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.036	0.005	0.000	0.026	0.046		-2.21
Dose OD						18.01	-39.86
_BD	-0.209	0.071	0.003	-0.348	-0.070	-5.78	12.79
_QDS	-0.442	0.074	0.000	-0.587	-0.297	-12.23	27.07
Mild ADR	-0.016	0.002	0.000	-0.020	-0.013	-0.45	
Severe ADR						11.80	-77.21
_rare	-0.410	0.069	0.000	-0.546	-0.274	-11.35	25.11
_uncommon	-0.851	0.062	0.000	-0.971	-0.730	-23.54	52.10
_cons	0.356	0.058	0.000	0.243	0.469		
No. of obs =	2034						
No. of groups =	226						
Wald chi^2 (6) =	317.150						
Log likelihood =	-1183.611						

Table A6.13
Unrestricted random-effects logit regression model for Netherlands: *Adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.045	0.007	0.000	0.032	0.058		-2.05
Dose OD						21.18	-43.36
_BD	-0.374	0.093	0.000	-0.556	-0.193	-8.32	17.04
_QDS	-0.578	0.102	0.000	-0.777	-0.379	-12.86	26.32
Mild ADR	-0.022	0.002	0.000	-0.026	-0.018	-0.49	
Severe ADR						13.23	-90.07
_rare	-0.573	0.090	0.000	-0.750	-0.396	-12.74	26.08
_uncommon	-1.405	0.094	0.000	-1.590	-1.221	-31.27	64.00
_cons	0.357	0.089	0.000	0.183	0.532		
No. of obs =	1502						
No. of groups =	175						
Wald chi^2 (6) =	308.030						
Log likelihood =	-768.444						

Table A6.14
Unrestricted random-effects logit regression model for Netherlands: *Non-adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.031	0.013	0.016	0.006	0.056		-0.93
Dose OD						5.69	-5.32
_BD	-0.142	0.182	0.435	-0.499	0.215	-4.64	4.33
_QDS	-0.032	0.183	0.859	-0.390	0.326	-1.06	0.99
Mild ADR	-0.033	0.005	0.000	-0.042	-0.024	-1.07	
Severe ADR						19.89	-66.34
_rare	-0.577	0.175	0.001	-0.920	-0.233	-18.82	17.59
_uncommon	-1.598	0.169	0.000	-1.930	-1.267	-52.16	48.75
_cons	0.614	0.190	0.001	0.241	0.987		
No. of obs =	480						
No. of groups =	56						
Wald chi^2 (6) =	112.300						
Log likelihood =	-228.816						

Table A6.15
Unrestricted random-effects logit regression model for Poland: *Adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.020	0.007	0.003	0.007	0.034		-1.04
Dose OD						51.46	-53.68
_BD	-0.273	0.102	0.007	-0.473	-0.073	-13.45	14.03
_QDS	-0.771	0.107	0.000	-0.981	-0.562	-38.01	39.65
Mild ADR	-0.019	0.003	0.000	-0.024	-0.015	-0.96	
Severe ADR						24.80	-73.84
_rare	-0.484	0.099	0.000	-0.678	-0.290	-23.85	24.87
_uncommon	-0.952	0.090	0.000	-1.129	-0.776	-46.94	48.96
_cons	0.444	0.089	0.000	0.269	0.619		
No. of obs =	1106						
No. of groups =	136						
Wald chi^2 (6) =	192.830						
Log likelihood =	-611.495						

Table A6.16
Unrestricted random-effects logit regression model for Poland: *Non-adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.035	0.006	0.000	0.023	0.047		-2.37
Dose OD						34.18	-81.01
_BD	-0.381	0.088	0.000	-0.555	-0.208	-10.81	25.62
_QDS	-0.824	0.096	0.000	-1.013	-0.636	-23.37	55.38
Mild ADR	-0.015	0.002	0.000	-0.019	-0.011	-0.42	
Severe ADR						15.62	-102.15
_rare	-0.536	0.087	0.000	-0.707	-0.365	-15.20	36.02
_uncommon	-0.984	0.082	0.000	-1.146	-0.823	-27.91	66.13
_cons	0.430	0.087	0.000	0.260	0.600		
No. of obs =	1457						
No. of groups =	176						
Wald chi^2 (6) =	236.740						
Log likelihood =	-808.973						

Table A6.17
Unrestricted random-effects logit regression model for Wales: *Adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.028	0.006	0.000	0.015	0.040		-0.81
Dose OD						31.40	-25.31
_BD	-0.356	0.091	0.000	-0.535	-0.177	-12.94	10.43
_QDS	-0.508	0.088	0.000	-0.680	-0.336	-18.46	14.87
Mild ADR	-0.034	0.002	0.000	-0.038	-0.030	-1.24	
Severe ADR						18.85	-49.21
_rare	-0.484	0.084	0.000	-0.650	-0.319	-17.61	14.19
_uncommon	-1.196	0.075	0.000	-1.343	-1.049	-43.46	35.02
_cons	0.503	0.069	0.000	0.367	0.639		
No. of obs =	1771						
No. of groups =	198						
Wald chi^2 (6) =	433.650						
Log likelihood =	-869.025						

Table A6.18
Unrestricted random-effects logit regression model for Wales: *Non-adherent sample*

Attribute	Coef	Std Err	P value	95% CI		MRS (%) Benefit	MRS (%) Mild ADR
Benefit	0.041	0.007	0.000	0.026	0.056		-1.39
Dose OD						21.30	-29.59
_BD	-0.322	0.106	0.002	-0.530	-0.114	-7.87	10.93
_QDS	-0.550	0.109	0.000	-0.763	-0.337	-13.43	18.66
Mild ADR	-0.029	0.003	0.000	-0.035	-0.024	-0.72	
Severe ADR						9.37	-44.88
_rare	-0.354	0.102	0.001	-0.555	-0.154	-8.65	12.02
_uncommon	-0.969	0.090	0.000	-1.145	-0.792	-23.66	32.86
_cons	0.378	0.087	0.000	0.207	0.548		
No. of obs =	1086						
No. of groups =	121						
Wald chi^2 (6) =	237.780						
Log likelihood =	-572.472						

Appendix 3.5 Short term treatment with antibiotics: patient questionnaire

Your Use of Antibiotics

Now, we would like to ask you several questions about the ANTIBIOTICS used for short-term conditions.

There are no right or wrong answers, please be as honest as possible.

1. **How long has it been since you were last prescribed an antibiotic (to be taken orally)?**

- Up to 12 months
- More than one year ago
- I am currently taking an antibiotic
- Never
- Don't remember

2. **For how many days were you prescribed that antibiotic?**

_____

3. **How many times a day you were supposed to take that antibiotic?**

- Once a day
- Two times a day
- Three times a day
- Four or more times a day
- Don't remember

4. **Did you obtain that antibiotic (e.g. from pharmacy)?**

- Yes
- No
- Don't remember

5. **If you did not obtain that antibiotic from pharmacy, what was the main reason for that?**

- I felt better
- I was afraid of side effects
- I was afraid that antibiotic could affect my immunity

- Cost
- I did not need it
- Other
- Don’t remember
- Not Applicable

6. **Did you start the treatment with that antibiotic?**

- Yes
- No
- Don’t remember

7. **If you did not start the treatment with that antibiotic, what was the main reason for that?**

- I felt better
- I was afraid of side effects
- I was afraid that antibiotic could affect my immunity
- To save it for future
- I did not need it
- Other
- Don’t remember

8. **When taking that antibiotic, have you stopped your treatment before the time scheduled by your doctor?**

- Yes
- No
- Don’t remember

9. **If you stopped your treatment before the time scheduled by your doctor, what was the main reason for that?**

- Forgetfulness
- I felt better
- Side effects
- Cost
- To save it for future
- Other

- Don’t remember

10. **When taking this antibiotic, have you skipped or missed one or more doses?**

- Yes
- No
- Don’t remember

11. If you skipped or missed one or more doses, what was the main reason for that?

- Forgetfulness
- I felt better
- Side effects
- Cost
- To save it for future
- Other
- Don’t remember

Appendix 4.1: Health psychology literature search strategies for electronic databases

MEDLINE via Pubmed

Health psychology search strategy

1. patient compliance [Majr]
2. treatment Refusal [Majr]
3. #1 OR #2
4. pharmaceutic*
5. prescript*
6. medicat*
7. medicament
8. medicine
9. medicines
10. drug
11. drugs
12. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. theory
14. theories
15. model
16. models
17. #13 OR #14 OR #15 OR #16
18. medication adherence report
19. MARS
20. Medication adherence questionnaire
21. Morisky
22. illness perception questionnaire
23. IPQ
24. brief illness perception questionnaire
25. brief IPQ
26. beliefs about medicines questionnaire
27. BMQ
28. theory of planned behaviour
29. TPB
30. beliefs and behaviours questionnaire
31. BBQ
32. health belief* model
33. HBM
34. life orientation test
35. LOT
36. life orientation test-revised

37. LOT-R
38. optimis*
39. self regulation theory
40. self regulation model
41. implementation intentions
42. perceived control
43. attitudes beliefs
44. subjective norm*
45. perceived behavioural control
46. motivation
47. necessity concerns
48. psychodynamic
49. cognitive behavi*
50. transtheoretical model
51. precede-proceed model
52. common-sense model
53. theory of reasoned action
54. purposeful action theory
55. social cognitive theory
56. self-efficacy
57. protection motivation theory
58. #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57
59. psycholog*
60. #58 OR #59
61. #3 AND #12 AND #17 AND #60
62. Limits : Animals, All infant : birth-23 months, All child : 0-18 years
63. 61 NOT 62

EMBASE

Health psychology search strategy

1. patient compliance/exp/mj
2. pharmaceutic*
3. prescript*
4. medicat*
5. medicament
6. medicine
7. medicines

8. drug
9. drugs
10. #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11. theory
12. theories
13. model
14. models
15. #11 OR #12 OR #13 OR #14
16. medication adherence report
17. MARS
18. Medication adherence questionnaire
19. Morisky
20. illness perception questionnaire
21. IPQ
22. brief illness perception questionnaire
23. brief IPQ
24. beliefs about medicines questionnaire
25. BMQ
26. theory of planned behaviour
27. TPB
28. beliefs and behaviours questionnaire
29. BBQ
30. health belief* model
31. HBM
32. life orientation test
33. LOT
34. life orientation test-revised
35. LOT-R
36. optimis*
37. self regulation theory
38. self regulation model
39. implementation intentions
40. perceived control
41. attitudes beliefs
42. subjective norm*
43. perceived behavioral control
44. motivation
45. necessity concerns
46. psychodynamic
47. cognitive behavi*

48. transtheoretical model
49. precede-proceed model
50. common-sense model
51. theory of reasoned action
52. purposeful action theory
53. social cognitive theory
54. self-efficacy
55. protection motivation theory
56. #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
57. psycholog*
58. #56 OR #57
59. #1 AND #10 AND #15 AND #58
60. Limits : Animals, All infant : birth-23 months, All child : 0-18 years
61. 59 NOT 60

CINANL

Health psychology search strategy

1. adherence
2. compliance
3. persistence
4. concordance
5. nonadherence
6. non-adherence
7. noncompliance
8. non-compliance
9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10. pharmaceutic*
11. prescript*
12. medicat*
13. medicament
14. medicine
15. medicines
16. drug
17. drugs
18. #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR 17
19. theory
20. theories

21. model
22. models
23. #19 OR #20 OR #21 OR #22
24. medication adherence report
25. MARS
26. Medication adherence questionnaire
27. Morisky
28. illness perception questionnaire
29. IPQ
30. brief illness perception questionnaire
31. brief IPQ
32. beliefs about medicines questionnaire
33. BMQ
34. theory of planned behaviour
35. TPB
36. beliefs and behaviours questionnaire
37. BBQ
38. health belief* model
39. HBM
40. life orientation test
41. LOT
42. life orientation test-revised
43. LOT-R
44. optimis*
45. self regulation theory
46. self regulation model
47. implementation intentions
48. perceived control
49. attitudes beliefs
50. subjective norm*
51. perceived behavioral control
52. motivation
53. necessity concerns
54. psychodynamic
55. cognitive behavi*
56. transtheoretical model
57. precede-proceed model
58. common-sense model
59. theory of reasoned action
60. purposeful action theory

61. social cognitive theory
62. self-efficacy
63. protection motivation theory
64. #24 OR #25 OR #26 OR#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63
65. psycholog*
66. #64 OR #65
67. #9 AND #18 AND #23 AND #66
68. Limits : Animals, All infant : birth-23 months, All child : 0-18 years
69. 67 NOT 68

PsychINFO

Health psychology search strategy

1. compliance
2. adherence
3. concordance
4. persistence
5. noncomplicance
6. non-compliance
7. nonadherence
8. non-adherence
9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10. pharmaceutic*
11. prescript*
12. medicat*
13. medicament
14. medicine
15. medicines
16. drug
17. drugs
18. #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR 17
19. theory
20. theories
21. model
22. models
23. #19 OR #20 OR #21 OR #22
24. medication adherence report
25. MARS

26. Medication adherence questionnaire
27. Morisky
28. illness perception questionnaire
29. IPQ
30. brief illness perception questionnaire
31. brief IPQ
32. beliefs about medicines questionnaire
33. BMQ
34. theory of planned behaviour
35. TPB
36. beliefs and behaviours questionnaire
37. BBQ
38. health belief* model
39. HBM
40. life orientation test
41. LOT
42. life orientation test-revised
43. LOT-R
44. optimis*
45. self regulation theory
46. self regulation model
47. implementation intentions
48. perceived control
49. attitudes beliefs
50. subjective norm*
51. perceived behavioral control
52. motivation
53. necessity concerns
54. psychodynamic
55. cognitive behavi*
56. transtheoretical model
57. precede-proceed model
58. common-sense model
59. theory of reasoned action
60. purposeful action theory
61. social cognitive theory
62. self-efficacy
63. protection motivation theory
64. #24 OR #25 OR #26 OR#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48

OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63

65. psycholog*
66. #64 OR #65
67. #9 AND #18 AND #23 AND #66
68. Limits : Animals, All infant : birth-23 months, All child : 0-18 years
69. 67 NOT 68

The Cochrane Library

Health psychology search strategy

1. MeSH descriptor **patient compliance** explode all trees
2. pharmaceutic*
3. prescript*
4. medicat*
5. medicament
6. medicine
7. medicines
8. drug
9. drugs
10. #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11. theory
12. theories
13. model
14. models
15. #11 OR #12 OR #13 OR #14
16. medication adherence report
17. MARS
18. Medication adherence questionnaire
19. Morisky
20. illness perception questionnaire
21. IPQ
22. brief illness perception questionnare
23. brief IPQ
24. beliefs about medicines questionnaire
25. BMQ
26. theory of planned behaviour
27. TPB
28. beliefs and behaviours questionnaire
29. BBQ
30. health belief* model

31. HBM
32. life orientation test
33. LOT
34. life orientation test-revised
35. LOT-R
36. optimis*
37. self regulation theory
38. self regulation model
39. implementation intentions
40. perceived control
41. attitudes beliefs
42. subjective norm*
43. perceived behavioral control
44. motivation
45. necessity concerns
46. psychodynamic
47. cognitive behavi*
48. transtheoretical model
49. precede-proceed model
50. common-sense model
51. theory of reasoned action
52. purposeful action theory
53. social cognitive theory
54. self-efficacy
55. protection motivation theory
56. #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
57. psycholog*
58. #56 OR #57
59. #1 AND #10 AND #15 AND #58
60. Limits : Animals, All infant : birth-23 months, All child : 0-18 years
61. 59 NOT 60

Appendix 4.2: Behavioural economics literature search strategies for electronic databases

MEDLINE via Pubmed

Health economics search strategy

1. patient compliance [Majr]
2. treatment Refusal [Majr]
3. #1 OR #2
4. pharmaceutic*
5. prescript*
6. medicat*
7. medicament
8. medicine
9. medicines
10. drug
11. drugs
12. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. theory
14. theories
15. model
16. models
17. #13 OR #14 OR #15 OR #16
18. consumer choice
19. rational consumer choice
20. consumer preference
21. rational choice model
22. utility
23. utility-function
24. price elasticity
25. expected utility
26. asymmetr* information
27. game theory
28. Nash equilibrium
29. Bargaining
30. time preference*
31. health capital
32. human capital
33. Grossman
34. prospect theory
35. discrete choice experiment
36. stated preference

37. random utility theory
38. Lancaster*
39. #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38
40. economic*
41. CBA [Majr]
42. 40 NOT 41
43. 39 OR 42
44. #3 AND #12 AND #17 AND #43
45. Limits : Animals, All infant : birth-23 months, All child : 0-18 years
46. 44 NOT 45
47. Limits: Publication Date from 1990/01/01 to 2010/01/01

EMBASE

Health economics search strategy

1. patient compliance/exp/mj
2. pharmaceutic*
3. prescript*
4. medicat*
5. medicament
6. medicine
7. medicines
8. drug
9. drugs
10. #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11. theory
12. theories
13. model
14. models
15. #11 OR #12 OR #13 OR #14
16. consumer choice
17. rational consumer choice
18. consumer preference
19. rational choice model
20. utility
21. utility-function
22. price elasticity
23. expected utility
24. asymmetr* information
25. game theory

26. Nash equilibrium
27. Bargaining
28. time preference*
29. health capital
30. human capital
31. Grossman
32. prospect theory
33. discrete choice experiment
34. stated preference
35. random utility theory
36. Lancaster*
37. #16 OR #17 or #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
38. economic*
39. cost effectiveness
40. cost utility
41. cost benefit
42. #39 OR #40 OR #41
43. 38 NOT 42
44. 37 OR 43
45. #1 AND #10 AND #15 AND #44
46. Limits : Animals, All infant : birth-23 months, All child : 0-18 years
47. 45 NOT 46
48. Limits: Publication Date from 1990/01/01 to 2010/01/01

CINANL

Health economics search strategy

1. adherence
2. compliance
3. persistence
4. concordance
5. nonadherence
6. non-adherence
7. noncompliance
8. non-compliance
9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10. pharmaceutic*
11. prescript*
12. medicat*
13. medicament

14. medicine
15. medicines
16. drug
17. drugs
18. #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR 17
19. theory
20. theories
21. model
22. models
23. #19 OR #20 OR #21 OR #22
24. consumer choice
25. rational consumer choice
26. consumer preference
27. rational choice model
28. utility
29. utility-function
30. price elasticity
31. expected utility
32. asymmetr* information
33. game theory
34. Nash equilibrium
35. Bargaining
36. time preference*
37. health capital
38. human capital
39. Grossman
40. prospect theory
41. discrete choice experiment
42. stated preference
43. random utility theory
44. Lancaster*
45. #24 OR #25 OR #26 OR#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44
46. economic*
47. cost effectiveness
48. cost utility
49. cost benefit
50. #47 OR #48 OR #49
51. #46 NOT #50
52. #45 OR 51

53. #9 AND #18 AND #23 AND #52
54. Limits : Animals, All infant : birth-23 months, All child : 0-18 years
55. 53 NOT 54
56. Limits: Publication Date from 1990/01/01 to 2010/01/01

EconLit

Health economics search strategy

1. compliance
2. adherence
3. concordance
4. persistence
5. noncomplicance
6. non-compliance
7. nonadherence
8. non-adherence
9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10. pharmaceutic*
11. prescript*
12. medicat*
13. medicament
14. medicine
15. medicines
16. drug
17. drugs
18. #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR 17
19. theory
20. theories
21. model
22. models
23. #19 OR #20 OR #21 OR #22
24. consumer choice
25. rational consumer choice
26. consumer preference
27. rational choice model
28. utility
29. utility-function
30. price elasticity
31. expected utility
32. asymmetr* information
33. game theory

34. Nash equilibrium
35. Bargaining
36. time preference*
37. health capital
38. human capital
39. Grossman
40. prospect theory
41. discrete choice experiment
42. stated preference
43. random utility theory
44. Lancaster*
45. #24 OR #25 OR #26 OR#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44
46. economic*
47. cost effectiveness
48. cost utility
49. cost benefit
50. #47 OR #48 OR #49
51. #46 NOT #50
52. #45 OR 51
53. #9 AND #18 AND #23 AND #52
54. Limits : Animals, All infant : birth-23 months, All child : 0-18 years
55. 53 NOT 54
56. Limits: Publication Date from 1990/01/01 to 2010/01/01

The Cochrane Library

Health economics search strategy

1. MeSH descriptor **patient compliance** explode all trees
2. pharmaceutic*
3. prescript*
4. medicat*
5. medicament
6. medicine
7. medicines
8. drug
9. drugs
10. #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11. theory
12. theories
13. model

14. models
15. #11 OR #12 OR #13 OR #14
16. consumer choice
17. rational consumer choice
18. consumer preference
19. rational choice model
20. utility
21. utility-function
22. price elasticity
23. expected utility
24. asymmetr* information
25. game theory
26. Nash equilibrium
27. Bargaining
28. time preference*
29. health capital
30. human capital
31. Grossman
32. prospect theory
33. discrete choice experiment
34. stated preference
35. random utility theory
36. Lancaster*
37. #16 OR #17 or #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
38. economic*
39. cost effectiveness
40. cost utility
41. cost benefit
42. #39 OR #40 OR #41
43. 38 NOT 42
44. 37 OR 43
45. #1 AND #10 AND #15 AND #44
46. Limits : Animals, All infant : birth-23 months, All child : 0-18 years
47. 45 NOT 46
48. Limits: Publication Date from 1990/01/01 to 2010/01/01

Appendix 4.3
Selected characteristics of studies presented in order of study design then quality assessment score from highest to lowest

First author *N [model n]*	Disease Medication	Age (SD) Male %	Adherence measure (time)[a]	Theory: model *Instrument/s* [b]	Key findings [c]	Quality [d]
Longitudinal studies						
Gonzalez[47] *N = 325 [325]*	HIV Antiretroviral	41 (8.5) 60	E: MEMS (>90%, 15-mths) S: ACTG	SRT: SRM *BMQ customised*	Structural Equation Model: Education* Pill burden* Symptoms* Necessity (specific)* Concerns (specific)* Distrust (general)*. Mediators: Distrust by concerns* Benefits by concerns* Benefits by necessity*.	27
Weaver[113] *N = 322 [322]*	HIV Antiretroviral	41(8.5) 58	E: MEMS (>90%, 15-mths) S: ACTG	SS: TMSC *COPE, SPS, ISEL*	Structural Equation Model: Age* Education, Income, Employment, Time since diagnosis* Regimen burden, Avoidant coping*. Mediators: Negative mood avoidant coping** SS by avoidant coping*.	27
Halkitis[52] *N = 300 [300]*	HIV Antiretroviral	42 (7.7) 100	E: MEMS (2-wks) S: Interview	SS: Coping/SE *Customised*	Structural Equation Model: Drug use* Socioeconomic status*. Mediators: Psychological state by drug use*.	27
Lynam[78] *N = 189 [189]*	HIV Antiretroviral	nr 73	E: MEMS (1-wk)	SRT: SDT *TSRQ, MHLC, SE-customised*	Structural Equation Model: MHLC Internal, MHLC: Chance, MHLC External** MHLC Powerful others, SE**. Mediators: Autonomous regulation by SE**.	27
Barclay [12] *N =185 [140]*	HIV Antiretroviral	44 (7.3) 78	E: MEMS (≥95%, 1-mth)	SCT: HBM ext. *ADQ, MHLC, SE-customised*	**Young** (n=140, age 41(5.0)) Drug abuse/dependence, Financial resource, Apathy/Indifference, MHLC Internal, MHLC Chance, SE* Perceived utility** Intention, Subjective norms, Support/Barriers. **Old** (n=45, age 56 (4.8)) Income, Sexual orientation, Global cognitive function* MHLC Internal, Subjective norms.	27
Stilley[104] *N = 158 [158]*	Cholesterol Lovastatin	46 (8.7) 54	E: MEMS (≥80%, 12-wks)	Distal: 5-FM *NEO PI-R*	Depression* Anxiety* Conscientiousness** IQ** Mental flexibility/Perceptual organisation.	27
Schmitz[98] *N = 97 [97]*	Smoking BupropionSR	49 (9.9) 0	E: MEMS (>50%, 7-wks)	SCT: HBM *HABQ*	Symptoms, Adherence feedback** Perceived barriers.	26
Apter[5] *N = 88 [85]*	Asthma Inhaled corticosteroids	47 (15) 28	E: MDILog[l] (42-days)	SCT: HBM/TRA *Customised*	Race/Ethnicity* Symptoms, Treatment Knowledge, Inhaled adherence scale, Attitude**.	26

First author *N [model n]*	Disease Medication	Age (SD) Male %	Adherence measure (time)[a]	Theory: model *Instrument/s* [b]	Key findings [c]	Quality [d]
Cohen[28] *N = 65 [57]*	Depression Antidepressant	41(11.4) 42	E: MEMS (14-wks)	Distal: 5-FM *NEO PI-R*	NEO PI-R Activity** NEO PI-R Feeling, NEO PI-R Modesty**.	26
Brus[16] *N = 65 [55]*	Rheumatoid Arthritis Sulphasalazine	59 (nr) 20	M: Pill count (≥80%, 3-mths)	SCT: SLT *Customised*	Age, Sex, Education, Health status, Symptoms, Disease severity, Patient education, SE** Barriers, Outcome expectation, Perceived social attitude, Perceived SS.	23
Abraham[1] *N = 176 [167]*	Malaria Mefloquine Chloroquine + Proguanil	nr (nr) 41 nr (nr) 34	S: Interview or questionnaire (at 6-7wks)	SCT: HBM/TPB *Customised*	**Mefloquine** (n=106) Adherence in malarious region, Perceived severity, Perceived susceptibility, Perceived side-effects* Perceived behavioural control(PBC), Intention** Attitude, Injunctive norm. **Chloroquine + Proguanil** (n=61) Adherence in malarious region** Perceived severity, Perceived susceptibility, Perceived side-effects, PBC, Intention, Attitude, Injunctive norm.	18
Simoni[101] *N = 136 [136]*	HIV Antiretroviral	43(8.9) 55	S: ACTG (at 3-mhs)	SS: *SSI, SBI*	Structural Equation Model: SE*. Mediators: Negative affect by SE** Spirituality by SE**.	18
Williams[114] *N = 186 [*126*]*	*Outpatients* *nr (≥ 1-mth)*	56 (nr) 25	S: Pill count (at 14-days)	SRT: SDT *MHLC, TSRQ, HCCQ*	Structural Equation Model: Autonomous motivation*. Mediators: Autonomy support by autonomous motivation*.	18
Lim[163] *N = 136 [126]*	Geriatric *poly-pharmacy*	81(8.1)/ 80 (7.7) 35	S: Interview (0 and 2-mths)	SCT: HBM *Customised*	Pharmacist intervention, Hospitalisation in last 6-mths, ADL, Responsibility for medicines taking, No. medication remembering methods, Barriers, Benefits, Severity*.	18
Farquharson[37] *N = 130 [94]*	Malaria Prophylaxis	37(13.1) 57	S: Interview (at 4.5-wks (4-7))	SCT: HBM/TPB *Customised*	**Full vs. Poor** (n=80) Benefits, Intentions, Length of stay, Info./questions, Adherence barriers discussion. **MLR: Full vs. Partial** (n=94) Benefits** Intentions, Length of stay** Info./questions* Adherence barriers discussion. **Partial vs. Poor** (n=40) Benefits, Intentions, Length of stay** Info./questions** Adherence barriers discussion.	18
Fraser[43] *N = 108 [104]*	Multiple sclerosis Glatiramer acetate	43 (8.8)/ 45 (9.5) 11	S: Interview or e-mail (dis/cont. at 6-mths)	SCT: Control Beliefs *MSSE, SES*	Individual hypotheses: SE total** SE control** SE function** Hope, Mobility** Spasticity** Fatigue-baseline*.	18

First author *N [model n]*	Disease Medication	Age (SD) Male %	Adherence measure (time)[a]	Theory: model *Instrument/s* [b]	Key findings [c]	Quality [d]
Turner[106] *N = 89 [85]*	Multiple sclerosis DMT	51(9.3) 80	S: Interview (per month for 6-mths)	SCT: HBM *ADQ, BACS*	**2-mth** (n=67) Age, Sex, Race , Yrs with MS , DMT type, Time on DMT, Cognitive status, Barriers, Benefits* Severity, Susceptibility. **4-mth** (n=80) Age* Sex, Race , Yrs with MS* DMT type, Time on DMT, Cognitive status, Barriers, Benefits* Severity* Susceptibility. **6-mth** (n=85) Age, Sex, Race , Yrs with MS , DMT type, Time on DMT, Cognitive status, Barriers, Benefits* Severity, Susceptibility.	17
Rudman[95] *N = 201 [190]*	Renal Immuno-suppressant	39(nr) 56	C: Laboratory report calls (over 12-mths)	SCT: PMT *Customised*	Structural Equation Model: Age at transplant* Side-effects complaints** MHLC External, SE** Threat appraisal* Protection motivation, Response costs, Response efficacy.	11
Cross-sectional studies						
Johnson[63] *N* = 244 [244]	HIV Antiretroviral	56 (4.8) 71	S: ACTG	SS: TMSC ext. *PSR, WOC, CWI*	Structural Equation Model: Time since diagnosis** Negative affect** Maladaptive coping** Perceived SS**.	18
George[45] *N = 819 [350]*	Heart failure *medication*	62 (12.6) 72	P: Refill data (≥90%, 14-mths)	SCT: HBM ext. *BMQ, MHLC and customised*	Born in North America, Smoker* Use of medications BD or less** Morisky score>0, Use of anti-depressants, Use of adherence aids, Self-reported adherence(%), Have you changed daily routine to accommodate your medication schedule** Perceived benefits .	15
Chisholm[23] *N* = 158 [158]	Renal Immuno-suppressant	51 (12.4) 60	P: Refill data (≥80%, 3-mths)	SCT: TPB *Customised*	Structural Equation Model Past behaviour ** Intention* Subjective norms, Perceived behavioural control, Attitude. Mediators: Attitudes by intentions, PBC by intentions.	15
Orensky[167] *N* = 125 [75]	Anti-coagulation Warfarin	60 (nr) 49	P: Refill data (≥80%, 6-mths) S: Questionnaire	SCT: HBM *Customised*	Structural Equation Model: (i) Prescription refill = Divorced/never married** Perceived barriers**. (ii) Self-report = Living in a shelter* Living with a friend or relative* Perceived barriers**.	14
Johnson[65] *N* = 2765 [2478]	HIV Antiretroviral	41/42 69	S: Computerised interview (≥90%, 3-days)	SRT: SAT *SPS and customised*	Race/Ethnicity** Current crack cocaine use* Injection use** Homeless/shelter* In primary relationship** Doses/day** SE** Symptom bother** Treatment beliefs* Coping SE** Necessity beliefs** SE-beliefs**.	13
Horne[59] *N* = 1871	IBD *maintenance therapies*	50 (16.0) 37	S: MARS	SRT: SRM *BMQ, IPQ-R chronicity only*	Age** Sex, Outpatient visits** GP visits, Inpatient visits, Time since diagnosis** Diagnosis , Attitudinal groups compared to accepting: Ambivalent** Indifferent** Skeptical**.	13

First author *N [model n]*	Disease Medication	Age (SD) Male %	Adherence measure (time)[a]	Theory: model *Instrument/s* [b]	Key findings [c]	Quality [d]
Greenstein[50] *N = 1402 [1223]*	Renal Immuno-suppressant	47 (12.5) 49	S: Questionnaire (previous 4-wks)	SRT: SRM *Customised*	Age** White collar** Time since transplant* Need drugs even if my kidney is functioning well* Drugs should never be delayed** Immunosuppresants stay active in my system for ≥24 hours*.	13
Byrne[19] *N* = 1611 [933]	Coronary Heart Disease *preventative*	66 (9.1) 65	S: MARS	SRT: SRM *BMQ, IPQ-R*	Age* Sex, General Medical Services eligible** GP consultations, Time since diagnosis, Previous MI, Cause-stress, Cause-heredity, Cause-own behaviour, Identity, Timeline-chronic** Consequences, Personal control, Treatment control, Coherence, Timeline-cyclical, Emotional representations, Necessity (spec)** Concerns (spec)** Harm (gen)** Overuse (gen)**.	12
De Smet[157] *N =1270[573]*	Asthma Inhaled corticosteroids	41 (2.4) 29	S: Questionnaire	SCT: HBM ext. *Customised*	SF-36 MCS, Years since diagnosis, Perceived barriers** Perceived benefits** Perceived severity** Enabling.	12
Johnson[67] *N* = 545 [545]	HIV Antiretroviral	43 (7.8) 81	S: ACTG (≥90%, 3-days)	SS: SP-S *SPS, SPSI-R*	Structural Equation Model: Age, Sex, Ethnicity, Alcohol, drug use, Psychological health**. Mediators: Constructive SP-S by Psychological Health** Dysfunctional SP-S by Psychological Health**.	12
Ross[93] *N* = 514	Hypertension Anti-hypertensive	60 (12.2) 52	S: Morisky	SRT: *BMQ, IPQ-R*	Age** Emotion** Personal control* Necessity (specific)**.	12
Chao[21] *N =1700[445]*	Diabetes (T2) Oral Hypo-glycaemic	56 (11.4) 50	S: Morisky / Horne 4-item	SCT: HBM ext. *Customised*	Structural Equation Model: Depression, SE** Perceived barriers** Perceived benefits, Perceived severity, Perceived susceptibility, Perceived side-effect barriers**.	12
Horne[57] *N* = 324	*Chronic Multiple*	nr (nr) [ii]	S: Questionnaire	SRT: *BMQ*	Age** Illness group: cardiac** Illness group: asthma** Necessity-concerns (differential)**.	12
Youssef[117] *N* = 316	Hypertension Anti-hypertensive	59 (9.2) 60	S: Questionnaire (≥90%, 1-mth)	SCT: HBM *Customised*	Controlled blood pressure** Restriction of dietary salt and fat** Perceived benefits** Perceived susceptibility ** Drug side-effects*.	12
Chen[22] *N* = 277	Hypertension Anti-hypertensive	66 (12.3) 60	S: Medication Adherence Inventory + *customised*	SRT: SRM *IPQ-R*	Age, Live alone* History hyperlipidaemia* /hypertension, SPB, Drug number, Identity, Symptoms after-yes, Symptoms after-uncertain, Timeline, -cyclical, Consequence, Personal control, Treatment control* Coherence, Emotional, Balanced, Psychological** Cultural, Risk*.	12

First author *N [model n]*	Disease Medication	Age (SD) Male %	Adherence measure (time)[a]	Theory: model *Instrument/s* [b]	Key findings [c]	Quality [d]
Gatti[44] *N* = 301 [275]	*Pharmacy patients not reported*	54(12.5) 27	S: Morisky	SRT: SRM *BMQ, SEAMS*	Age<65yrs** Literacy level of less than high school, Self-report of hyperlipidaemia * Low SE** BMQ (score ≥47)**.	12
Phatak[170] *N* = 250	*Chronic Multiple*	nr (nr)[iii] [i]38	S: Morisky	SRT: SRM *BMQ*	Age** Conditions, Medications(n)* Necessity (specific)* Concerns (specific)** Harm (general), Overuse (general).	12
Brown[15] *N = 300 [241]*	Hypertension Anti-hypertensive	62 (nr) 31	S: Interview (last 30-days)	SCT: HBM *Customised*	Age* Sex, Education, Poverty status, Perceived barriers-forgetting** Perceived barriers-refill, Perceived benefits, Perceived side-effect barriers**.	12
Clatworthy[27] *N = 259 [223]*	BPD Antimanic	48(11.2) 36	S: MARS	SRT: SRM *BMQ*	Age, Sex, Age of diagnosis, Medications (n), Depression, Symptoms, Necessity (specific)** Concerns (specific)**.	12
Roh[177] *N* = 219 [219]	Hypertension Anti-hypertensive	65 (8.5) 61	S: Hill-Bone Compliance to High Blood Pressure Therapy Scale	SRT: SAT *GSES, PRA, KHS, MOS-SSS*	Structural Equation Model: Knowledge, SE*. Mediators: Depression by SE* SS by relationship and SE*	12
Cha[20] *N* = 215	HIV Antiretroviral	41 (7.6) 67	S: Morisky	SS: *ISEL*	Structural Equation Model: SE**. Mediators: Depression by SE** Perceived SS by self-efficacy beliefs**.	12
Sud[178] *N = 238 [*208*]*	Acute Coronary Syndromes	65(13.0) 61	S: Medication Adherence Scale	SRT: SRM *BMQ*	Age, Sex, Race, Education, Number of other people, Heart-related health status** Co-morbidities, Necessity (specific)** Concerns (specific), Harm (general), Overuse (general).	12
Nageotte[85] *N* = 260 [202]	*Chronic mental health* Neuroleptic	35 (8.8) 68	S: Interview	SCT: HBM *Customised*	Sex , Race, Marital status, Urban/rural residence, Perceived barriers** Perceived benefits, Perceived threat* Perceived side-effect barriers.	12
Kennedy[71] *N =205 [201]*	HIV Antiretroviral	40 (nr) 85	S: Interview P: Refill data for verification n=40	SRT: SDT *HCCQ, TSRQ, + SE*	Structural Equation Model: Psychological distress** Perceived competence** Autonomous motivation mediated by perceived competence** Autonomous support mediated by psychological distress**.	12

First author *N [model n]*	Disease Medication	Age (SD) Male %	Adherence measure (time)[a]	Theory: model *Instrument/s* [b]	Key findings [c]	Quality [d]
Ponieman[171] *N = 259 [*201]	Asthma Inhaled corticosteroids	48 (13) 18	S: MARS	SRT: SRM *BMQ*	SE** Necessity (specific)** Concerns (specific)** Regimen hard to follow*.	12
Amico[4] *N = 200 [200]*	HIV Antiretroviral	39 (8.9) 65	S: ACTG-*reversed*	SCT: IMB *IMB questionnaire*	Structural Equation Model: Adherence Behavioural Skills*. Mediators: Adherence information by adherence behavioural skills* Adherence motivation by adherence behavioural skills*.	12
Richardson[174] *N = 201 [*197*]*	Hypertension Anti-hypertensive	54 (13.1) 22	S: Interview C: Blood Pressure	SCT: HBM *Customised*	Age* Duration of treatment* Salt restriction, Low net barriers, Medium net barriers* Perceived barriers*.	12
Pomeroy[90] *N = 225 [184]*	HIV Antiretroviral	43(7.3) 78	S: Medication Adherence Scale	SCT: IMB ext. *SSRS + customised*	Children in household, Medical care within 1-yr of diagnosis, Receiving mental health services* Intention** Information** Motivation- vulnerability* Motivation-provider, Perceived SS.	12
Cox[29] *N* = 179	HIV Antiretroviral	37 (7.7) 91	S: Patient rated and clinician rated	SS: *Customised*	Discriminant Function Analysis: Employment* Symptoms* Emotional support (actual)*.	12
Brewer[14] *N* = 169	High cholesterol *cholesterol-lowering*	67 (10) 61	S: Questionnaire C: Blood cholesterol	SRT: SRM *Customised*	Age, Sex, Ethnicity, Education, Smoker, CHD, Hypertension, Diabetes, Medication side-effects** Number of medications , Consequences* Timeline, Cause, Cure, Symptoms.	12
Valeberg[181] *N* = 164 [140]	Cancer Analgesic	58 (11.4) 21	S: Questionnaires	SCT: HBM ext *Customised*	Sex, Average pain score, Opioid or other pain medication** Pain relief** SE**.	12
Kopelowicz[74] *N* = 155	Schizophrenia Anti-psychotic	34(10.8) 63	S: Treatment Compliance Interview	SCT: TPB *TPB Inventory*	Perceived behavioural control**Attitude, Subjective norms**.	12
Mann[80] *N* = 151 [150]	T2 Diabetes PO Hypo-glycaemic	57 (11) 55	S: Morkisy	SRT: SRM *IPQ, BMQ +Customised SE*	SE* Necessity (specific), Concerns (specific)* Disease beliefs* Regimen hard to follow*.	12

First author *N [model n]*	Disease Medication	Age (SD) Male %	Adherence measure (time)[a]	Theory: model *Instrument/s* [b]	Key findings [c]	Quality [d]
Ferguson[38] *N = 149 [149]*	HIV Antiretroviral	39(8.6) 87	S: PMAQ [part 1]	SCT: HBM *barriers only* PMAQ [part 2]	*KAMED* Qualities of Medicine Schedule and Memory score* SS, Qualities of medicine* Schedule* Memory*.	12
Sajatovic[96] *N* = 140 [140]	BPD Antimanic	43 (11.2) [iv] 50	S: Tablets Routine Questionnaire	SCT: Attitudes/ control *AMSQ, ITAQ, MHLC*	Age, Sex,Ethnicity, Education, Drug addiction** Illness duration, Psychiatric rating scale, Depression, Clinical Global Impression* ISEL, MHLC Internal, MHLC Chance, MHLC Powerful others* AMSQ** ITAQ** Rating of Medication Influences (ROMI)**.	12
Bane[11] *N* = 139	Hypertension Anti-hypertensive	52(12.1) 51	S: Questionnaire	SCT: SE / TPB *Customised*	Perceived behavioural control** Intention, Attitude** Subjective norms.	12
Atkinson[7] *N = 137 [130]*	HIV Antiretroviral	40(6.8) 74	S: ECAB	SS: TMSC *ECAB*	Structural Equation Model: SE* Optimism* Social isolation. Mediators: Stress by optimism* Psychological distress by patient-doctor relationship and optimism* SS by SE*.	12
Holstad[55] *N* = 120 [115]	HIV Antiretroviral	37(8.5) 60	S: Antiretroviral General Adherence Scale	SCT: HBM/TRA *ADQ adapted*	Sex, Alcohol, Years HIV** Existential well-being, Perceived severity, Support/Barriers**.	12
Schmid-Mohler[200] *N* = 114 [110]	Renal Immuno-suppressant	54 (11.9) 65	S: BAASIS C: Nurse / Doctor reports	SCT: IMBP *Customised*	Barrier-feeling overwhelmed, Barrier-practical difficulties during intake, Barrier-no medication aids, Barrier-forgetfulness/interruption of daily routine* Intention.	12
Hekler[53] *N = 139 [*102*]*	Hypertension Anti-hypertensive	62 (10.2) 34	S: Interview	SRT: SRM *Customised*	Age* Sex, BMI, Education, Marital status, Time since diagnosis, Consequences, Timeline, Identity, Timeline-cyclical, Control/ cure beliefs, Disease cause/control.	12
Horne[58] *N = 119 [100]*	Asthma Inhaled corticosteroids	49 (18.8) 39	S: MARS	SRT: SRM *IPQ, BMQ*	Age, Sex, Education, No. family doctor visits, Number of asthma-related hospital admissions* Duration of asthma, Consequences** Timeline, Identity, Cure, Necessity (specific)** Concerns (specific)**.	12
Starace[103] N = 100 [100]	HIV Antiretroviral	39 (7.3) 69	S: ACTG	SCT: IMB *IMB questionnaire*	Structural Equation Model: Adherence Behavioural Skills*. Mediators: Adherence information by adherence behavioural skills* Adherence motivation by adherence behavioural skills*.	12

First author *N [model n]*	Disease Medication	Age (SD) Male %	Adherence measure (time)[a]	Theory: model *Instrument/s* [b]	Key findings [c]	Quality [d]
van Servellen[110] *N* = 85 [77]	HIV Antiretroviral	40 (8.9) 90	S: ACTG	SS: *MOS-SSS + customised*	Months of antiretroviral treatment, Treatment Knowledge, Depression, SE, Emotional support (actual)* Patient-provider relationship**.	11
Frain[40] *N = 76 [76]*	HIV Antiretroviral	30-39 81	S: Questionnaire	SS: FRT *FIRM*	CD4 count, Health worries, Financial worries, Disclosure worries, Life satisfaction* Provider trust** Overall functioning, Medication concerns (QoL item), Sexual functioning, Global distress, HIV mastery** Optimism* Uncertainty, Family resiliency.	11
Muma[166] *N = 66 [52]*	HIV Antiretroviral	nr (nr)[v] 83	S: Questionnaire C: Erythrocytes	SCT: HBM *Customised*	Ethnicity** Perceived barriers-problems taking and scepticism about medication*.	11
Simoni[102] *N* = 50 [50]	HIV Antiretroviral	41 (8.0) 38	S: ACTG	SS: *SSI + customised*	Depression** Anxiety* SE, SS (actual), Perceived SS , Treatment knowledge.	11
Fraser[42] *N* = 594 [199]	Multiple Sclerosis Glatiramer acetate	46 (nr) 24	C: Record review (continued/dis-continued at 1-yr)	SCT: Control Beliefs *MSSE, SES*	Individual hypotheses: SE control* SE function** Hope, Self-esteem, Perceived support from spouse* Perceived support from physician*.	8
Christensen[154] *N = 112 [72]*	Renal *not reported*	46 (nr) 54	C: Serum K levels / Serum P levels	Distal: 5-FM *NEO Five-factor Inventory*	Age* Conscientiousness*.	8
Budd[151] N = 40 [40]	Schizophrenia Neuroleptic	49 (nr) 75	C: Accepted medication (>33%, 12-mths)	SCT: HBM Customised	Discriminant Function Analysis: Benefits, Severity, Perceived susceptibility**.	8

Note. **Disease:** *BPD* borderline personality disorder, *DMT disease modifying therapy, HIV* human immunodeficiency virus, *IBD* inflammatory bowel disease. **Adherence measures:** ACTG Adherence to Combination Therapy Guide, BAASIS Basel Assessment of Adherence Scale for ImmunoSuppressives, *ECAB* Elicitation of Compliance and Adherence Behaviours Questionnaire, *MARS* Medication Adherence Rating Scale, *MEMS* Medication Event Monitoring System, *PMAQ* Patient Medication Adherence Questionnaire. **Theory/models:** *SCT* Socio-cognitive theory, SRT Self-regulation theory, *SS* Social Support: 5-FM five factor model, *FRT* family resiliency theory, *HBM* health belief model, *IMB* Information motivation and behavioural skills, *IMBP* integrated model of behavioural prediction, *PMT* protection motivation theory, *SAT* social action theory, SDT Self-determination Theory, SE self-efficacy, *SLT* social learning theory, *SP-S* social problem-solving, *SRM* self-regulation model, *TMSC* transactional model of stress and coping, *TPB* theory of planned behaviour, *TRA* Theory of Reasoned Action. **Instruments:** ADQ Adherence Determinants Questionnaire, ADQ Antiretroviral Adherence Determination, AMSQ Attitudes towards Mood Stabilisers Questionnaire, BACS Barriers to Care Scale Questionnaire, BMQ Beliefs about Medicines Questionnaire, *COPE* COPE Inventory, *CWI* Coping with Illness Scale, *FIRM* Family Inventory of Resources for Management, *GSES* General Self-efficacy Scale, *HABQ* Health Awareness and Beliefs Questionnaire, *HCCQ* Health Care Climate Questionnaire, *IPQ(-R)* Illness Perceptions Questionnaire (Revised), *ISEL* Interpersonal Support Evaluation List, *ITAQ* Insight and Treatment Attitudes Questionnaire, *KHS* Knowledge of Hypertension Scale, *MHLC* Multi-dimensional Health Locus of Control, *MOS-SSS*

Medical Outcomes Study Social Support Survey, *MSSE* MS Self-efficacy Scale, *NEO PI-R* NEO Personality Inventory, *PMAQ* Patient Medication Adherence Questionnaire, *PRA* Patient Reactions Assessment, *PSR* Provision of Social Relations Scale, *SBI* System of Belief Inventory, *SCI* Self as Carer Inventory, *SEAMS* Self-efficacy for Appropriate Medication Use Scale, *SES* Rosenberg Self-Esteem Scale, *SPS* Social Provisions Scale, *SPSI-R* Social Problem Solving Inventory-Revised, *SSI* UCLA Social Support Inventory, *SSRS* Social Support and Reciprocity Scale, *TSRQ* Treatment Self-regulation Questionnaire, *WOC* Ways of Coping Questionnaire.
[a] Adherence measures categorised as: *E* electronic device*, M* mediation measurement, *P* prescription records*, S* self-report, *C* clinical indicator/proxy. [b] Primary model and instrument/s used to test primary model only. [c] Regression model unless otherwise stated.
*p≤.05, **p≤.01

[i] Westmed, Inc, Englewood, Colo, US
[ii] Disease: n, mean age (SD), % mail: Asthma n=78, 46 (18.3), 37. Renal n=47, 49 (17.3), 49. Cardiac n=116, 64 (12.4), 71. Oncology n=83, 59 (15.8), 51.
[iii] Presented in groups (n(%)) <30 28(11.2); 30-39 35(14.0); 40-19 93 (37.2); 50-59 61(24.4); ≥60 33(13.2).
[iv] Mean (sd) of adherent group, non-adherent (n=27) 41 (11.7)
[iv] Presented in groups (%) <26 7.7; 26-30 28.8; 31-35 25.0; 36-40 13.5; 41-45 13.5; >11.5.

Appendix 4.4 Behavioural economics papers: study characteristics

Reference	Participant characteristics	Study characteristics	Adherence measure
Atella et al. 2006	Disease: Hypertension Medicine: Anti-hypertensives n: 38393; mean age: 67.9 yrs; % male: 46.78	Aim: To investigate if and how health policy changes affect compliance Design: Natural experiment [panel data]	Prescription records: electronic databases [drug prescription, hospitalisation, and death and transfer registries] Unit: adherence ratio: dispensed to prescribed doses; Threshold: >= 0.55
Balu et al. 2009	Disease: Dyslipidemia Medicine: Cholesterol lowering n: 8988; mean age: 52.98 yrs; % male: 75.3	Aim: To compare medication adherence between patients initiating fixed-dose combination versus multi-pill combination dyslipidemia therapies Design: Retrospective cohort	Prescription records: refill data Unit: medication possession ratio; Threshold: 0.8
Bhosle et al. 2007	Disease: Glaucoma Medicine: Prostaglandin analogue [Latanoprost] n: 268; mean age: 77.6 yrs; % male: 33.1	Aim: To examine the medication use behaviours associated with the introduction of latanoprost therapy in a treatment-naive older population Design: Retrospective cohort	Prescription records: refill data Unit: medication possession ratio;
Boyer et al. 2009	Disease: HIV Medicine: ART n: 532; mean age: 38 yrs; % male: 29.1	Aim: To assess the extent to which user fess for antiretroviral therapy represent a financial barrier to access to ART among HIV-positive patients in Yaoundé, Cameroon Design: Cross-sectional	Self-report: patient questionnaire Unit: List of questions dichotomized to Low/moderate and high adherence;

Reference	Participant characteristics	Study characteristics	Adherence measure
Chapman et al 2001	Disease: Hypertension & High cholesterol Medicine: Anti-hypertensives & cholesterol-lowering agents n: 195; 169; mean age: 79.2; 67 yrs; % male: 35; 61	Aim: To examine the relationship between scenario measures of time preference and preventative health behaviours Design: Cross-sectional	Multiple: Self-report & clinical indicator:- Patient questionnaire Pill count symptomology [blood pressure] symptomology [blood pressure] patient questionnaire [ROMI] symptomology [cholesterol level] Unit:- adherence ratio: consumed pills to target mm Hg mm Hg difference in measured LDL count from NCEP target; Threshold: No deviations SBP < 140 & DBP < 90 SBP < 140 & DBP < 90
Cole et al.2006	Disease: CHF Medicine: Beta blockers(i) or ACE inhibitors (ii) n: 10403 (i) 5259; (ii) 5144; mean age: (i) 65.7; (ii) 65.1 yrs; % male: (i) 57.6); (ii) 56.0	Aim: To measure the association among prescription copayment, drug adherence, and subsequent health outcome among patients Design: Retrospective cohort	Prescription records: national health insurance plan database Unit: MPR (medication possession ratio) ;
Gibson 2006	Disease: High cholesterol & hyperlipidemia Medicine: Cholesterol-lowering [statins] n: (i) 142341 new; (ii) 92344 continuing; mean age: (i) 57; (ii) 64.1 yrs; % male: (i) 51.3; (ii) 55.4	Aim: To assess the effects of statin copayments on statin adherence among individuals with employer-based insurance Design: Cross-sectional	Prescription records: electronic database [MedStat MarketScan] Unit: medication possession ratio [%]; Threshold: >= 80%

Reference	Participant characteristics	Study characteristics	Adherence measure
Gregoire et al. 2002	Disease: Hypertension Medicine: Anti-hypertensives n: 682; mean age: 58.3 yrs; % male: 45	Aim: To examine the effect of an array of potential predisposing, enabling and reinforcing factors on the discontinuation of initial antihypertensive medication Design: Prospective cohort	Self-report: interview Unit: not reported;
Hsu et al. 2006	Disease: Various: hypertension, hyperlipidemia, & diabetes Medicine: within each disease group n: 199179; mean age: ~74 yrs; % male: 41	Aim: To compared the clinical and economic outcomes in 2003 among Medicare+ Choice beneficiaries whose annual drug benefits were capped at $1,000 and beneficiaries whose drug benefits were unlimited because of employer supplements Design: Prospective cohort	Prescription records: electronic database [administrative claims] Unit: % derived from ratio; Threshold: >=80%
Jackson et al. 2004	Disease: Various: hypertension, diabetes, heart failure, & IHD Medicine: within each disease group n: 3073; mean age: ~74 yrs; % male: 46	Aim: To study the relationship among prescription benefit status, health, and medication acquisition in a sample of elderly HMO enrolees with 1 or more common, chronic conditions Design: Cross-sectional	Prescription records: refill data Unit: not reported;
Kephart et al.2007	Disease: Various: Type 2 diabetes, dyspepsia & gastroesophageal reflux Medicine: Antisecretory & hypoglycaemics n: 61737 per month; mean age: not reported yrs; % male: not reported	Aim: To test the hypothesis that deductibles (copayment combined with annual limits on out-of-pocket payments) may reduce the effect of copayments on drug use for patients who expect to reach the annual limit, using as a natural experiment the introduction of copayments with an annual maximum to the seniors' drug plan in Nova Scotia Design: Cross-sectional	Prescription records: electronic database [Nova Scotia Seniors' Pharmacare Program (NSSPP)] Unit: not reported

Reference	Participant characteristics	Study characteristics	Adherence measure
Kurlander et al. 2009	Disease: Diabetes and chronic pain Medicine: Hypoglycaemics & analgesics n: 245; mean age: 55 yrs; % male: 28	Aim: To examine how cost and non-cost factors are associated with patterns of cost-related non-adherence (CRN) to medications Design: Cross-sectional	Self-report: interview Unit: not reported
Lummis et al.2008	Disease: Stroke Medicine: Anti-hypertensive n: 420; mean age: 68.2 yrs; % male: 55.7	Aim: To examine factors associated with persistence in patients following strokes Design: Cross-sectional	Self-report: Unit: yes/no for still taking medication
McDonnell et al.2001	Disease: Tuberculosis Medicine: Anti-tuberculosis therapy n: 62; mean age: 46.5 yrs; % male: 70.97	Aim: To identify antecedents of adherence to antituberculosis therapy Design: Cross-sectional	Self-report: tuberculosis adherence determination questionnaire (TBADQ)
Mishra et al.2005	Disease: Tuberculosis Medicine: Antibiotics n: 135; mean age: 39.94 yrs; % male: 75.57	Aim: To analyse the contribution of socio-economic status to non-adherence to DOTS Design: Retrospective cohort	Prescription records: medical records Unit: months where treatment is interrupted; Threshold: No 2 consecutive months of treatment
Rodin et al.2009	Disease: IHD & diabetes Medicine: not specified n: 8787; mean age: 56.03 yrs; % male: 63.4	Aim: To evaluate the effect on adherence of a pharmacy benefit change that included free generic drugs and higher copayments for brand-name drugs Design: Cross-sectional	Prescription records: refill data Unit: Medicine possession ratio; Threshold: 0.8

Reference	Participant characteristics	Study characteristics	Adherence measure
Silva et al.2009	Disease: HIV Medicine: ART n: 412; mean age: 36 yrs; % male: 69.2	Aim: To identify risk factors for non-adherence to antiretroviral therapy in Brazil Design: Cross-sectional	Self-report: Unit: % of doses taken
Thiebaud et al. 2008	Disease: Various Medicine: Statins n: 17798; mean age: 50.3 yrs; % male: 53.7	Aim: To determine the effect of copay change on compliance Design: Cross-sectional	Prescription records: drug utilization Unit: % of months where the number of days of drugs supplied exceeds a threshold (ii) average number of days of drugs supplied per month; Threshold: 5, 15, 25
Wang et al.2008	Disease: Mental health: Depression Medicine: Anti-depressants n: 71390; mean age: 75.7 yrs; % male: 30.6	Aim: To study the effect on adherence of two sequential cost-sharing policies in British Columbia seniors Design: Cross-sectional	Prescription records: drug utilization & refill data Unit: (i) number of imipramine-equivalent milligrams dispensed per month; (ii) % of patients continuing with therapy per month; Timeframe: Threshold: nonpersistence: failing to refill a prescription within 90 days of exhausting available supply
Ye et al.2007	Disease: IHD Medicine: Statins n: 5548; mean age: 63 yrs; % male: 67	Aim: To examine the relationship between copayment and adherence to statin treatment amongst patients who initiated statin treatment after discharge from a CHD hospitalization Design: Cross-sectional	Prescription records: refill data Unit: medication possession ratio; Threshold: MPR >= 80%
Zeber et al.2007	Disease: Various Medicine: not specified n: 80668; mean age: 52.8 yrs; % male: 95	Aim: To assess the effect of the 2002 Veterans Milennium Health Care Act, which raised pharmacy copayments from $2 to $7 for lower-priority patients on medication refill decisions Design: Cross-sectional	Prescription records: refill data Unit: number of fills

Reference	Participant characteristics	Study characteristics	Adherence measure
Zhang et al.2007	Disease: Hypertension Medicine: Anti-hypertensives n: 1351; mean age: 55.9 yrs; % male: 58.2	Aim: To quantify the relationship between amount of prescription cost-sharing and medication refill persistence Design: Cross-sectional	Prescription records: refill data Unit: number of days without medication in first 6 months of treatment; Threshold: 0.8

Appendix 4.5 Behavioural economics papers: study model & results – data extraction

Reference	Behavioural model & components tested	Model measure	Results	Model prediction *(if reported)*
Atella et al. 2006 Rank: 21 Disease: Hypertension Medicine: Anti-hypertensives n: 38393; mean age: 67.9 yrs; % male: 46.78 Consumer demand theory	Consumer demand theory: Price: copayment Quantity: prescription items	Review of drug prescription, hospitalisation, and death & transfer registries during Italian Health Service policy changes: Policy 0: Flat €1.5 per prescription Policy 1: Abolition of copayment Policy 2: Reduction from 6 to 3 of the maximum number of packages for each prescription Policy 3: Reintroduction of copayment €1 per prescription n: 18626 Length of follow-up: 6 years	For low compliants (ratio <0.55): Policy 0: Compliance = 0.356 Policy 1: Compliance = 0.570 Policy 2: Compliance = 0.532 Policy 3: Compliance = 0.481 High compliants (ratio >=0.55): Policy 0: Compliance = 0.923 Policy 1: Compliance = 0.901 Policy 2: Compliance = 0.817 Policy 3: Compliance = 0.789 Significance only reported for health outcomes and mortality. Authors summarise that the results show that drug co-payments has a strong effect on compliance, and this effect is immediate.	

Reference	Behavioural model & components tested	Model measure	Results	Model prediction *(if reported)*
Balu et al. 2009 Rank: 26 Disease: Dyslipidemia Medicine: Cholesterol lowering n: 8988; mean age: 52.98 yrs; % male: 75.3 Consumer demand theory	Consumer demand theory: Price: copayments Substitution effects: generic/brand	HealthCore Integrated Research Database:- $10 increase in copayment n: 2463 Length of follow-up: 1 year	NER/S: 0.6870 (p value < 0.0001) NER/L: 0.6060 (p value < 0.0001) Age (1 year increase): 1.0210 (p value <0.0001) Female: 0.7430 (p value < 0.0001) Baseline copayment ($10 increase): 0.9980 (p value = 0.032) Pre-index date angina: 1.3180 (p value < 0.0001) Pre-index data hypertension: 1.2390 (p value < 0.0001) Deyo-Charlson comorbidity score: 0.9560 (p value = 0.0968) Odds ratios < 1 indicate less likely to be compliant	
Bhosle et al. 2007 Rank: 35 Disease: Glaucoma Medicine: Prostaglandin analogue [Latanoprost] n: 268; mean age: 77.6 yrs; % male: 33.1 Consumer demand theory	Consumer demand theory: Demand	Study data n: 268 (100 treatment, 168 control) Length of follow-up: 2 years	Age = 0.05 Age^2 = -0.00033 Male = -0.055 Latanoprost = 0.057 (p value < 0.01) Total number of prescribed medications = -0.003 (p value < 0.05) Combination therapy = 0.21 Constant = -1.90 Reference group is control, female, no combination therapy	Adjusted R^2 = 0.052

Reference	Behavioural model & components tested	Model measure	Results	Model prediction *(if reported)*
Boyer et al. 2009 Rank: 66 Disease: HIV Medicine: ART n: 532; mean age: 38 yrs; % male: 29.1 Consumer demand theory	Consumer demand theory: Budget constraints	Questionnaire - Dichotomized by "During the last 3 months, were you ever unable to buy your HIV medicines because of lack of money?" n: 532 Length of follow-up: N/A	% of patients with no financial difficulties in purchasing ART who had good adherence - 63.4% % of patients with financial difficulties in purchasing ART who had good adherence - 29.9% p value < 0.0001	
Chapman et al 2001 Rank: 66 Disease: Hypertension & High cholesterol Medicine: Anti-hypertensives & cholesterol-lowering agents n: 195; 169; mean age: 79.2; 67 yrs; % male: 35; 61 Time preference	Health time preference Financial time preference	Interview n: 128 Length of follow-up: n/a	Health time preference: 0.17 (p < 0.06) Financial time preference: -0.04	R^2 = 0.05 for full model

Reference	Behavioural model & components tested	Model measure	Results	Model prediction *(if reported)*
Cole et al. 2006 Rank: 26 Disease: CHF Medicine: Beta blockers(i) or ACE inhibitors (ii) n: 10403 (i) 5259; (ii) 5144; mean age: (i) 65.7; (ii) 65.1 yrs; % male: (i) 57.6); (ii) 56.0 Consumer demand theory	Consumer demand theory:	Copayment n: (i) 5259; (ii) 5144 Length of follow-up: n/a	(i) A $10 increase in copayment was associated with a 2.6% decrease in MPR (95% CI: 2.0-3.1%) (ii) A $10 increase in copayment was associated with a 1.8 decrease in MPR (95% CI: 1.4-2.2%)	

Reference	Behavioural model & components tested	Model measure	Results	Model prediction *(if reported)*
Gibson 2006 Rank: 26 Disease: High cholesterol & hyperlipidemia Medicine: Cholesterol-lowering [statins] n: (i) 142341 new; (ii) 92344 continuing; mean age: (i) 57; (ii) 64.1 yrs; % male: (i) 51.3; (ii) 55.4 Consumer demand theory	Consumer demand theory: Price: copayment Demand Utility maximisation	Copayment n: 142341 new users, 92344 continuing users Length of follow-up: 4 years	New users: $10 increase in copayment: 3% decrease in odds of adherence ($p < 0.01$) 100% increase in copayment: 1.2% decrease in odds of adherence For continuing users, there was no significant association between higher copayments and adherence	
Gregoire et al. 2002 Rank: 26 Disease: Hypertension Medicine: Anti-hypertensives n: 682; mean age: 58.3 yrs; % male: 45 Consumer demand theory	Consumer demand theory: Income effect	Questionnaire n: 682 Length of follow-up: N/A	Hazard ratio for discontinuation: Family annual income (Canadian dollars) 40,000 or more: 1 (default) 20000-39999: 0.96 (0.71-1.30) 0-19999: 1.14 (0.85-1.53)	

Reference	Behavioural model & components tested	Model measure	Results	Model prediction *(if reported)*
Hsu et al. 2006 Rank: 19 Disease: Various: hypertension, hyperlipidemia, & diabetes Medicine: within each disease group n: 199179; mean age: ~74 yrs; % male: 41 Consumer demand theory	Consumer demand theory: Price	Patient record data: Whether or not subjects had a $1,000 cap on drug benefits n: 199179 Length of follow-up: 1 year	Odds ratios for drug non-adherence for capped as opposed to non-capped benefits: Antihypertensive drugs: 1.30 (1.23-1.38) Lipid-lowering drugs: 1.27 (1.19-1.34) Antidiabetic drugs: 1.33 (1.18-1.48)	
Jackson et al. 2004 Rank: 45 Disease: Various: hypertension, diabetes, heart failure, & IHD Medicine: within each disease group n: 3073; mean age: ~74 yrs; % male: 46 Consumer demand theory	Consumer demand theory: Income effect	Questionnaire n: 3073 Length of follow-up: n/a	CMG: Annual Income: Less that $20,000: 0.13 (0.11,0.15) $20,000 - $50,000: 0.10 (0.09,0.11) $50,000 or more: 0.10 (0.07,0.13)	

Reference	Behavioural model & components tested	Model measure	Results	Model prediction *(if reported)*
Kephart et al. 2007 Rank: 35 Disease: Various: Type 2 diabetes, dyspepsia & gastroesophageal reflux Medicine: Antisecretory & hypoglycaemics n: 61737 per month; mean age: not reported yrs; % male: not reported Consumer demand theory	Consumer demand theory: Price: copayments	Policy changes in Nova Scotia: Copayments (None, $3 per prescription or 20% of of prescription cost) Prob of exceeding copayment threshold ($150) n: 61,737 per month Length of follow-up: 3.5 years	Odds ratios for drug use: Prob exceed copay threshold low: Introduction $3 copay: H2RA: 0.970 (0.960-0.978) OHA: 0.990 (0.984-0.996) Change to 20% copayment: H2RA: 0.994 (0.985-1.003) OHA: 1.011 (1.005-1.017) Prob exceed copay threshold high: No significant differences Effect on mean quantity of medication use: Prob exceed copay threshold low: Introduction $3 copay: H2RA: 5% decrease ($p < 0.001$) OHA: 5% decrease ($p < 0.001$) Change to 20% copayment: H2RA: 15% decrease ($p < 0.001$) OHA: 12% decrease ($p < 0.001$) Prob exceed copay threshold high: No significant differences	

Reference	Behavioural model & components tested	Model measure	Results	Model prediction *(if reported)*
Kurlander et al. 2009 Rank: 66 Disease: Diabetes and chronic pain Medicine: Hypoglycaemics & analgesics n: 245; mean age: 55 yrs; % male: 28 Consumer demand theory	Consumer demand theory: Income effects Price: Monthly medication costs (MMC)	Questionnaire n: 128 Length of follow-up: n/a	Odds ratios for cost-related non-adherence: Diabetes: Income < $20000: 2.11 (0.82-5.47) MMC > $50: 1.86 (0.71-4.83) Pain: Income < $20000: 9.06 (2.44-33.60) MMC > $50: 2.11 (0.67-6.64) Diabetes: Income < $20000: 5.74 (1.58-20.88) MMC > $50: 3.90 (1.29-11.78)	
Lummis et al. 2008 Rank: 66 Disease: Stroke Medicine: Anti-hypertensive n: 420; mean age: 68.2 yrs; % male: 55.7 Consumer demand theory	Consumer demand theory: Price: monthly drug cost	Estimated from patient's discharge medication list n: 420 Length of follow-up: 6 months	Odds ratios for persistence: Monthly drug costs >= $200.00: 1 (default) $90.00 <= monthly drug costs < $200.00: 5.25 (1.14,24.25) Monthly drug costs < $90.00: 6.74 (1.32,34.46)	

Reference	Behavioural model & components tested	Model measure	Results	Model prediction *(if reported)*
McDonnell et al. 2001 Rank: 137 Disease: Tuberculosis Medicine: Anti-tuberculosis therapy n: 62; mean age: 46.5 yrs; % male: 70.97 Consumer demand theory	Consumer demand theory: Income effects	Questionnaire Questionnaire Questionnaire TBADQ TBADQ TBADQ n: 62 Length of follow-up: N/A	Significant correlation (p = 0.04) between adherence and an annual income of $11,000 or more Regression model: Intercept: 22.2 Alcohol: -3.67 Income: 0.53 Education: 0.49 Intentions: 0.19 Supports/barriers: 0.18 Self-care agency: -0.005	Full model explains 28% of the variance
Mishra et al. 2005 Rank: 35 Disease: Tuberculosis Medicine: Antibiotics n: 135; mean age: 39.94 yrs; % male: 75.57 Consumer demand theory	Consumer demand theory: Income effects Price: travel Budget constraints	Questionnaire n: 135 Length of follow-up: 8 months	Odds ratios: Annual income: Higher (>100,000 Nepalese rupees): 1 (default) Medium (50,000-100,000 Nepalese rupees): 3.9 (0.8-19.0) Lower (<50,000 nepalese rupees): 6.3 (1.3-29.2) Travel cost to TB treatment facility: No: 1 (default) Yes: 3.2 (1.5-7.1) Difficulty in financing treatment: No: 1 (default) Yes: 2.6 (1.1-5.9)	

Reference	Behavioural model & components tested	Model measure	Results	Model prediction *(if reported)*
Rodin et al. 2009 Rank: 45 Disease: IHD & diabetes Medicine: not specified n: 8787; mean age: 56.03 yrs; % male: 63.4 Consumer demand theory	Consumer demand theory: Price: copayments Substitution effects: generic/brand	Policy change in Minnesota:- Elimination of $5 copayment charge for generic drugs Increase from $30 to $35 in the copayment for brand-name drugs n: 8787 Length of follow-up: 4 years	% change in adherence. Overall includes people who changed between branded and generic drugs Statins: Generic: 18.2 (p = 0.26) Brand: 1.2 (p = 0.65) Overall: 4.9 (p = 0.03) Sulfonylureas: Generic: -0.3 (p = 0.93) Brand: -1.6 (p = 0.82) Overall: 0.6 (p = 0.82) Metformin: Generic: 2.4 (p = 0.25) Brand: -1.9 (p = 0.8) Overall: 2.3 (p = 0.26) Thazolidinediones: Brand: -1.9 (p = 0.56) Insulin: Brand: -0.6 (p = 0.85)	
Silva et al. 2009 Rank: 66 Disease: HIV Medicine: ART n: 412; mean age: 36 yrs; % male: 69.2 Consumer demand theory	Consumer demand theory: Income effects	Questionnaire n: 412 Length of follow-up: N/A	Odds ratios: Family income (multiple of minimum wage) >7: 1 (default) 4-6: 1.08 (0.43-2.69) 1-3: 2.01 (0.99-4.17) <1: 1.95 (0.65-5.80) p value for significance: 0.08	

Reference	Behavioural model & components tested	Model measure	Results	Model prediction *(if reported)*
Thiebaud et al. 2008 Rank: 35 Disease: Various Medicine: Statins n: 17798; mean age: 50.3 yrs; % male: 53.7 Consumer demand theory	Consumer demand theory: Price: copayments Substitution effects: generic/brand (ii) Price: copayment Supply	Pharmacy data n: 17798 Length of follow-up: n/a	Odds ratio, prob of exceeding threshold with $1 increase in copayment: 5 day threshold: Brand: 0.991 (p < 0.0001) Generic: 0.993 (p = 0.2343) 15 day threshold: Brand: 0.991 (p = 0.0015) Generic: 0.993 (p = 0.2227) 25 day threshold: Brand: 0.998 (p = 0.4422) Generic: 1.004 (p = 0.4881) (ii) % change in supply from a $1 increase in copayment: Brand: -0.9 (p < 0.0001) Generic: -1.6 (p < 0.0001)	

Reference	Behavioural model & components tested	Model measure	Results	Model prediction *(if reported)*
Venturini et al. 1999 Rank: 35 Disease: Type II diabetes Medicine: Sulfonylureas n: 786; mean age: 59 yrs; % male: 50.9	Patient-related attributes Drug regimen characteristics & complexity Health status & disease-related variables Characteristics of the interaction with healthcare providers	Questionnaires: RAND short-form [SF] 36; Morisky; demographic and patient satisfaction items n: 786 Length of follow-up:	OLS Estimates of factors predictive of compliance (n=786) B Estimate (SE) *p<0.001, **p<0.05, ***p<0.01 Intercept = 0.790 (0.078)* Demographics: Age = 0.002 (0.001)** Gender (1=female) = 0.024 (0.015) Race (1=non-white) = -0.028 (0.015) Education (1=at least high school) = 0.017 (0.021) Work status (1 = employed) = 0.011 (0.018) Marital status (1= married) = 0.016 (0.016) Self-report compliance (1=high compliance) = 0.031 (0.015)** Self-perception of health status: General health = -0.003 (0.001)* Vitality = 0.002 (0.001) Social functioning = 0.002 (0.001) Physical functioning = -0.001 (0.001) Bodily pain = -0.001 (0.001) Mental health = -0.001 (0.001) Role emotional = 0.001 (0.001) Role physical = 0.001 (0.001) Drug regimen complexity:- Antidiabetic medication doses (n) = -0.061 (0.006)* Second generation sulfonylureas (1=yes) = 0.036 (0.016)** Insulin (1=yes) = 0.016 (0.011) Other chronic medications (n) = 0.001 (0.003) Health status:- Hospital days (n) = -0.001 (0.002) Duration (1=newly treated patient) = -0.066 (0.024)*** Chronic disease score = 0.001 (0.005) Patient-provider encounter:- Satisfaction with physician's advice = 0.012 (0.005) Satisfaction with pharmacist's encounter = -0.015 (0.015) Outpatient visits (n) = -0.001 (0.001) Single pharmacy patronage = -0.010 (0.015) Model F-value = 6.26** Adjusted R^2 = 0.148	R^2=0.148

Reference	Behavioural model & components tested	Model measure	Results	Model prediction *(if reported)*
Wang et al. 2008 Rank: 35 Disease: Mental health: Depression Medicine: Anti-depressants n: 71390; mean age: 75.7 yrs; % male: 30.6 Consumer demand theory	Consumer demand theory: Price: copayments	Based on changes to the British Columbia health system: There were two policy changes. First, the change from full prescription coverage to $10-$25 copayments. Secondly, the replacement of copayments with income-based deductibles and 25% coinsurance n: 71390 Length of follow-up: 8 years	Baseline use (Jan 1997): 76,043 Baseline trend per month: 857 (p < 0.001) Level change after copay start: -1,910 (p = 0.47) Trend change after copay per month: 375 (p = 0.13) Level change after IBD versus copay: -982 (p = 0.72) Trend change after IBD per month versus copay: -626 (p = 0.02) Level change after IBD versus baseline: 2,498 (p = 0.25) Trend change after IBD per month versus baseline: -282 (p = 0.003) Antidepressant utilization is expressed in imipramine-equivalent milligrams per 1,000 seniors per month (ii) Baseline use (Jan 1998): 13.17 Baseline trend per month: -0.03 (p = 0.004) Level change after copay start: 0.02 (p = 0.98) Trend change after copay per month: -0.05 (p = 0.37) Level change after IBD versus copay: 0.32 (p = 0.57) Trend change after IBD per month versus copay: 0.09 (p = 0.14) Level change after IBD versus baseline: -0.46 (p = 0.51) Trend change after IBD per month versus baseline: 0.04 (p = 0.18) Proportion of antidepressant users who discontinued their medication each month	

Reference	Behavioural model & components tested	Model measure	Results	Model prediction *(if reported)*
Ye et al. 2007 Rank: 45 Disease: IHD Medicine: Statins n: 5548; mean age: 63 yrs; % male: 67 Consumer demand theory	Consumer demand theory: Price	Prescription data n: 5548 Length of follow-up: n/a	Odds ratios: Copayment < $10: 1 (default) $10-$20: 0.97 (0.85-1.11) >$20: 0.44 (0.38-0.51) p value < 0.001	
Zeber et al. 2007 Rank: 35 Disease: Various Medicine: not specified n: 80668; mean age: 52.8 yrs; % male: 95 Consumer demand theory	Consumer demand theory: Price	2002 Millennium Health Care Act: Increase in copayment from $2 to $7 for lower-priority patients n: 80668 Length of follow-up: n/a	Difference in average total pharmacy fills per patient between groups: Copay exempt-$2 copayment: -3.19 Copay exempt-$7 copayment: -5.56 $2 copayment-$7 copayment: -2.37 Medical fills: Copay exempt-$2 copayment: -0.97 Copay exempt-$7 copayment: -3.45 $2 copayment-$7 copayment: -2.48 Psychiatric fills: Copay exempt-$2 copayment: -3.85 Copay exempt-$7 copayment: -4.12 $2 copayment-$7 copayment: -0.25 All of these differences are significant	

Reference	Behavioural model & components tested	Model measure	Results	Model prediction *(if reported)*
Zhang et al. 2007 Rank: 45 Disease: Hypertension Medicine: Anti-hypertensives n: 1351; mean age: 55.9 yrs; % male: 58.2 Consumer demand theory	Consumer demand theory: Price	Prescription data n: 1351 Length of follow-up: n/a	A $10 increase in copayment was associated with: An 18.9% (7.3-30.4) increase in total number of days without medication. A 31.9% (12.0-55.3) increase in the prob of being non-adherent A 10% (1-19) increase in the prob of having a gap of 30 days or longer	

Appendix 5.1 Pharmaceutical company initiatives to improve medication adherence in Europe: questionnaire

This survey is being conducted as a part of Ascertaining Barriers to Compliance, a research project funded by the European Commission's 7th Framework Programme to conduct research to determine that state of the science in medication adherence, assess the current state of adherence initiatives, and develop practice and policy recommendations for medication adherence throughout the European Union.

One of our goals is to develop an inventory of methods used by the pharmaceutical industry to promote patient adherence to medications. We are asking all members of the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Generic Medicines Association (EGMA) to participate.

This information will be combined with inventories of national and international medication adherence guidelines and of adherence education programs in European health professional training programs (e.g., medical, nursing, and pharmacy schools). The results will be reported to the European Commission and disseminated to project stakeholders. The identities of the respondents and their companies will be kept confidential, and will not appear in any ABC Project report or publication. **No information will be disclosed that can be linked to any particular company.** The survey will take only about 5 minutes to complete.

1. Please enter the name of your company.

2. Are medication adherence interventions currently addressed in your pharmaceutical company's strategic plan?

- ○ Yes
- ○ No

3. If Yes, please indicate how it is addressed (this could include pasting the relevant section in the box below, and/or a link to web-based material, where available).

4. At what levels does your company currently support or provide initiatives to enhance medication adherence? (Check all that apply)

- ☐ Global
- ☐ Regional (e.g., Europe, Asia-Pacific, etc.)
- ☐ National/Country

- [ ] Local (within country)

5. Does your company currently have a dedicated division or staff addressing medication compliance/adherence? If so, under what department? (Check all that apply)

- [ ] No dedicated compliance/adherence staff
- [ ] Medical
- [ ] Marketing
- [ ] Research/Drug Development
- [ ] Outcomes Research

6. For what patient populations does your company currently have programs to improve medication adherence? (Check all that apply)

- [ ] Adult
- [ ] Pediatric

7. For what types of medications does your company currently have programs to improve patients' medication adherence? (Check all that apply)

- [ ] All conditions/products
- [ ] Allergy/Cold/ENT
- [ ] Analgesics
- [ ] Antimicrobials/Anti-infectives
- [ ] Asthma/Pulmonary
- [ ] Cardiovascular
- [ ] Dermatologic
- [ ] Endocrine/Metabolic conditions
- [ ] Gastrointestinal
- [ ] Genitourinary
- [ ] Hematology/Oncology
- [ ] Immunologics/Immunosuppressives
- [ ] Neurologic

☐ Nutrition/Electrolytes

☐ Obstetrics/Gynecology

☐ Ophthalmic agents

☐ Psychiatric

☐ Rheumatologic

☐ Other

8. For which target groups does your company develop or provide interventions to improve medication adherence? (Check all that apply)

○ Development of intervention materials or programs for patients

○ Development of intervention materials or programs for healthcare professionals

○ Development of community-based intervention strategies (e.g., public health, population-based initiatives)

○ Provide funding to researchers for adherence intervention research

9. Please indicate the methods your company currently uses to promote patient adherence to prescribed medication regimens targeting patients, family members, or other caregivers (Check all that apply):

	Patients	**Family members/Caregivers**
Development of written materials promoting medication knowledge and medication adherence	○	○
Development of videos/DVDs to promote medication adherence among patients	○	○
Publication of drug-specific instructions for patients about what to do if a dose is missed	○	○
Development of less complex medication regimens with fewer daily doses	○	○
Development of combination drugs to improve medication adherence	○	○
Development of patient-friendly drug delivery systems	○	○
Establishment of patient assistance programs to improve accessibility to medication for patients with financial need	○	○
Use of adherence-enhancing packaging methods	○	○

	Patients	Family members/Caregivers
Distribution of reminder systems, pill organizers, etc.	○	○
Providing telephone adherence support to patients	○	○
Providing text message (SMS) reminders	○	○
Providing internet-based interventions	○	○
Interventions targeting individuals with limited financial resources	○	○
Interventions targeting patients with low literacy	○	○
Interventions targeting racial or ethnic minorities	○	○
Interventions targeting adolescents	○	○
Interventions targeting older adults/elderly	○	○
Other (please specify in the box below)	○	○

Please provide any detail possible for the methods you have indicated above. This may include descriptions, links to websites with more information, etc.

10. Please indicate the methods your company currently uses to promote patient adherence through initiatives targeting healthcare professionals: (Check all that apply)

- ○ Development of health care professional-focused reading materials on how to address medication adherence
- ○ Development of videos/DVDs to train health care professionals in methods for addressing medication adherence with patients
- ○ Development of training sessions or workshops for health care professionals to improve skills at addressing medication adherence
- ○ Publication of drug-specific instructions for health care professionals to use when counseling patients who have missed doses
- ○ Providing pharmacy refill tracking systems to health care providers to monitor patients' medication adherence
- ○ Other (please specify)

11. Does your company have any new medication adherence initiatives planned for the next 12 months?

◉ Yes

○ No

12. If yes, would you please be so kind as to provide a description of the planned initiative(s) (without compromising any confidential information), with a link to any web-based material, if available:

13. Our report would benefit from additional information or exemplars to illustrate the pharmaceutical industry's efforts to improve patient adherence. If you would be willing to be contacted to provide additional information, please provide your contact information in the space below.

Thank you for taking the time to participate in this survey. The information you have provided will help us in our mission to develop medication adherence practice and policy recommendations for the EU.

If you have any additional information or descriptive materials that you would like to provide to better illustrate your company's initiatives to improve medication adherence, please send them to pharmasurvey@abcproject.eu

Appendix 5.2: Survey of European health care professional educational programs' content on managing medication adherence: questionnaire

Medication non-adherence (also commonly called non-compliance) has been identified as a significant barrier to achieving optimal clinical outcomes from prescribed medications. As a result, the European Commission, through the 7th Framework Programme, commissioned the Ascertaining Barriers to Compliance (ABC) Project to conduct research to determine the state of the science in medication adherence, assess the current state of adherence initiatives, and develop practice and policy recommendations for medication adherence throughout the European Union.

One of the ABC Project's goals is to assess methods used by schools of medicine, pharmacy, and nursing to train health care providers to assess and manage patient adherence to medications. We are inviting you and your institution to participate.

This information will be combined with inventories of national and international medication adherence guidelines and of pharmaceutical industry initiatives to promote improved medication adherence. The results will be reported to the European Commission and disseminated to project stakeholders. The identities of the respondents and their institutions will be kept confidential, and will not appear in any ABC Project report or publication. **No information will be disclosed that can be linked to any particular institution.** The survey will take only about 5 minutes to complete.

1. Please enter the name of your institution. **(This is used only to track responses and for making country-specific comparisons.)**

2. Please tell us more about your institution (check all that apply).

- ☐ School of Medicine
- ☐ School of Pharmacy
- ☐ School of Nursing

3. In what type of institution is your school/department based?

- ☐ Based in a university
- ☐ Based in a vocational or technical school

4. Does your school's curriculum currently contain specific content on how to *assess* medication adherence? (please check all that apply)

☐ Didactic/classroom/lecture

☐ Clinical/practicum/hands-on skills training

☐ Case studies

☐ Medication adherence is not addressed

☐ Other (please specify)

5. Does your school's curriculum contain specific content on how to *improve or promote* medication adherence? (please check all that apply)

☐ Didactic/classroom/lecture

☐ Clinical/practicum/hands-on skills training

☐ Case studies

☐ Medication adherence is not addressed

☐ Other (please specify)

6. Approximately how many contact hours of didactic (classroom) training or instruction do your students receive regarding the assessment and management of medication adherence?

7. Approximately how many contact hours of clinical (practicum/hands-on) training do your students receive regarding the assessment and management of medication adherence?

8. For which target groups does your adherence training content recommend interventions to improve medication adherence? (Check all that apply)

○ Patients

○ Families/caregivers

○ Community-based intervention strategies (e.g., public health, population-based initiatives)

9. Please indicate the methods your institution currently recommends to students to promote patient adherence to prescribed medication regimens targeting patients, family members, or other caregivers (Check all that apply):

	Interventions for Patients	**Interventions for Family members/Caregivers**

	Interventions for Patients	Interventions for Family members/Caregivers
Face-to-face education	○	○
Printed educational materials	○	○
Goal-setting	○	○
Feedback		
Prescription of combination drugs to improve medication adherence	○	○
Prescription of less complex medication regimens with fewer daily doses	○	○
Motivational interviewing	○	○
Use of reminder systems, pill organizers, etc.	○	○
Targeting interventions to individuals with limited financial resources	○	○
Targeting interventions to patients with low literacy	○	○
Targeting interventions to racial or ethnic minorities	○	○
Targeting interventions to adolescents	○	○
Targeting interventions to older adults/elderly	○	○
Other (please specify in the box below)	○	○

Please provide any detail possible for the methods you have indicated above. This may include descriptions, links to websites with more information, etc.

10. At what level does your program offer this adherence education? (please check all that apply)

- ○ Bachelor's
- ○ Master's

11. Does your institution have plans to start any new medication adherence training initiatives in the next 12 months?

- ○ Yes
- ○ No

If yes, would you please be so kind as to provide a description of the planned initiative(s), with a link to any web-based material, if available:

12. Our report would benefit from additional information or exemplars to illustrate educational programs to improve training for health care providers regarding patient adherence. If you would be willing to be contacted to provide additional information, please provide your contact information in the space below.

Thank you for taking the time to participate in this survey. The information you have provided will help us in our mission to develop medication adherence practice and policy recommendations for the EU.

If you have any additional information or descriptive materials that you would like to provide to better illustrate your institution's initiatives to improve medication adherence education and training, please send them to educationsurvey@abcproject.eu

Appendix 5.3 Healthcare professional survey questionnaire

Screen 2: Eligibility filter

Introductory Questions

Welcome to the ABC Survey of Health Care Professionals. We are delighted that you have decided to take part in this survey. Thank you for your time.

Please begin by completing the questions below.

After answering the questions, go to the next screen by clicking the NEXT button at the bottom.

1. Are you a [1]

☐ Doctor

☐ Pharmacist

☐ Nurse

☐ None of the above **[→screen 10]**

2. Are you qualified and registered to practice? [1]

☐ Yes

☐ No **[→screen 10]**

3. Do you work with adults? [1]

☐ Yes

☐ No **[→screen 10]**

4. Do you work in the community/ primary care? [1]

☐ Yes

☐ No **[→screen 10]**

5. Do you have direct patient contact? [1]

☐ Yes

☐ No **[→screen 10]**

>>NEXT>>

Screen 3: Introduction

Thank you for taking the time to participate in this survey. We are very grateful for your time.

We are really interested in finding about your views on medication adherence. This survey is not about the general views or ethos of the organisation you work for, or what you feel your views about adherence ought to be. Rather, we are interested in YOUR ACTUAL views about medication adherence.

There are no right or wrong answers so please just make your best guess.

The questionnaire is divided into six (6) sections; please complete all of the questions in each section in relation to your CURRENT AND MAIN post. All questions concern your interactions with patients regarding their PRESCRIBED MEDICATIONS. The questions are also specific to your discussions with ADULT patients with LONG TERM conditions. The questionnaire includes the following sections:

A. **Information about you**
B. **The extent of nonadherence to medication in patients**
C. **Your beliefs about adherence to prescribed medication**
D. **Your use of adherence enhancing interventions**
E. **Barriers to your use of adherence enhancing interventions**
F. **Questions about training and guidelines**

>>NEXT>>

Screen 4a: Information about you

First, we would like to ask you questions about yourself.

After answering the questions, go to the next screen by clicking the NEXT button at the bottom.

1. **What is your profession?**

O Doctor O Pharmacist O Nurse

2. **How many years have you been registered as a qualified healthcare professional?**

O less than 1 year
O 1 – 5 years
O 6 – 10 years
O 11 – 15 years
O over 15 years

3. **What is your gender?**

O Male O Female

4. **How old are you?** Please enter your age in years

<<PREVIOUS<< >>NEXT>>

Screen 4b: Information about you (continued)

5. Which health care setting do you mainly work in?

O Community hospital
O Family medicine/general practice
O Specialist community service
O Care/nursing home
O Community pharmacy/dispensary
O Community nursing team
O Polyclinic
O Other (please describe)…….

6. What type of healthcare organisation do you mainly work in?

(This question does not concern your own employment arrangements, but rather the nature of the organisation(s) you work in)

O Privately funded organisation
O State funded organisation
O Insurance/Sick fund funded
O Other funding arrangement (please describe) ……

7. On average, how long do you spend talking with patients about their use of medications? (*Please give the average amount of time you spend discussing a patient's use of prescribed medications in any one interaction, in minutes, for patients with a chronic illness.)*

O no time at all
O less than 1 minute
O 1 - 5 minutes
O 6 - 10 minutes
O 11 - 15 minutes
O more than 15 minutes

<<PREVIOUS<< >>NEXT>>

Screen 5a: The extent of nonadherence to medication in patients

The next few questions are in two parts across two screens. The first set of questions concern your perceptions about nonadherence in ALL patients in your country. The second screen in this section includes questions regarding your perceptions about YOUR OWN patients and their level of adherence to medication.

So first, this section asks questions about your perception of nonadherence in ALL patients with a chronic condition in your country.

We are interested in YOUR views. Remember, there are no right or wrong answers, so just make your best guess.

After answering the questions, go to the next screen by clicking the NEXT button at the bottom.

1. What percentage of ALL PATIENTS with a chronic condition/illness IN YOUR COUNTRY do you think do NOT initiate prescribed medication (that is, patients who do NOT take ANY of their prescribed medication)?

O 0-15% O 16 - 35% O 36 - 65% O 66 - 85% O 86-100%

2. What percentage of ALL PATIENTS with a chronic condition/illness IN YOUR COUNTRY and who initiate their prescribed medication, DO take their medicines as prescribed?

O 0-15% O 16 - 35% O 36 - 65% O 66 - 85% O 86-100%

3. What percentage of ALL PATIENTS with a chronic condition/illness IN YOUR COUNTRY and who initiate their prescribed medication, DO persist with their medication for 1 year?

O 0-15% O 16 - 35% O 36 - 65% O 66 - 85% O 86-100%

<<PREVIOUS<< >>NEXT>>

Screen 5b: The extent of nonadherence to medication in patients (continued)

This next section asks questions about YOUR PERCEPTION of nonadherence in YOUR patients with a chronic condition.

After answering the questions, go to the next screen by clicking the NEXT button at the bottom.

1. What percentage of patients THAT YOU SEE with a chronic condition/illness, do you think do NOT initiate prescribed medication (that is, patients who do NOT take any of their prescribed medication)?

O 0-15% O 16 - 35% O 36 - 65% O 66 - 85% O 86-100%

2. What percentage of patients THAT YOU SEE with a chronic condition/illness, and who initiate their prescribed medication, DO take their medicines as prescribed?

O 0-15% O 16 - 35% O 36 - 65% O 66 - 85% O 86-100%

3. What percentage of patients THAT YOU SEE with a chronic condition/illness, and who initiate their prescribed medication, DO persist with their medication for 1 year?

O 0-15% O 16 - 35% O 36 - 65% O 66 - 85% O 86-100%

<<PREVIOUS<< >>NEXT>>

Screen 6: Your beliefs about adherence to prescribed medication

Please indicate to what extent you agree or disagree with each of the following statements about patient adherence. (Please click only one option in each row).

After answering the questions, go to the next screen by clicking the NEXT button at the bottom.

		Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strogly Agree	Don't know
1	Patients' beliefs about whether or not they need medication affect their adherence to treatment.						
2	Patients' concerns about their medication affect their adherence to treatment.						
3	Most nonadherence is intentional.						
4	Most nonadherence is unintentional.						
5	It is possible to improve patient adherence to medication.						
6	There is not one specific intervention for improving adherence which is suitable for everyone.						
7	Patients have the right to refuse or to stop taking medication providing they have the capacity to make informed decisions.						

<<PREVIOUS<< >>NEXT>>

Screen 7a: Your use of adherence enhancing interventions

What assessment strategies and interventions do YOU use to increase patient adherence to medication use?

This section of questions is about what you do to support patients with adherence to medications. It may be the case that other colleagues in your organisation, or other services that you know of, support patients with their medications. We are concerned here only with the strategies and interventions that YOU use in your day to day practice.

Remember that these questions are just about patients with a chronic illness or long term condition.

Please select from the drop down menu in the LEFT COLUMN which best represents how often YOU USE this assessment strategy/intervention.

If the assessment strategy is not appropriate for your role (for example, the item refers to discussing a medication with a patient before it is prescribed, and you only see patients after a medication is prescribed) then please choose the option 'not applicable'. If the intervention is relevant to your role, please choose one of the options that best describes how often you use it- never, occasionally, sometimes, frequently, all the time.

For every assessment strategy/intervention YOU USE, please mark in the RIGHT COLUMN how EFFECTIVE you think this strategy/intervention is.

If you responded 'not applicable' for a particular strategy/intervention, you do not need to answer this question and can move on to the next item.

After answering the questions, go to the next screen by clicking the NEXT button at the bottom.

		Do you use this intervention?						**If used, in your opinion, is this intervention effective?**			
		Never	Occasionally	Sometimes	Frequently	All the time	Not applicable	Not at all	Somewhat	Extremely	Don't know
	Assessment of adherence and its risk factors										
1	I ask patients if they										

	have missed any doses of their medication [1]										
2	I ask patients if they have reduced the dose of their medication										
3	I ask patients if they have changed their medication regimen										
4	I take blood or urine samples to assess patient's level of adherence										
5	I use standardised questionnaires/screening tools to assess patient's level of adherence										
6	I use electronic monitoring devices to assess patient's level of adherence										
7	I use pill counts to assess patient's level of adherence or pill counts										
8	I speak to the patient's family, friends or carers to assess patient's level of adherence										

<<PREVIOUS<< >>NEXT>>

Screen 7b: Your use of adherence enhancing interventions (continued)

		Do you use this intervention?						**If used, in your opinion, is this intervention effective?**			
		Never	Occasionally	Sometimes	Frequently	All the time	Not applicable	Not at all	Somewhat	Extremely	Don't know
	Providing information for patients/carers										
9	I offer patients information about their condition/illness										
10	I offer patients information about treatment options for their condition/illness										
11	I offer patients information about the medication they are prescribed										
12	I offer patients information about how they might benefit from taking their prescribed medication(s)										
13	I offer patients information about side effects and how to deal with them										
14	I check that patients understand the information that I have given them										
15	I provide patients with written (paper based) information about their medication										
16	I provide patients with video tapes/DVD/audio/computer materials about their medication										
17	I offer educational/support classes and peer mentoring to patients										

<<PREVIOUS<< >>NEXT>>

Screen 7c: Your use of adherence enhancing interventions (continued)

		Do you use this intervention?						**If used, in your opinion, is this intervention effective?**			
		Never	Occasionally	Sometimes	Frequently	All the time	Not applicable	Not at all	Somewhat	Extremely	Don't know
	Talking with patients about their medications										
18	I ask patients what level of involvement they would like in making decisions about their treatment										
19	I give patients the opportunity to ask any questions about their condition or illness										
20	I give patients the opportunity to ask questions about their medication										
21	I address any beliefs or concerns that patients may have which have resulted in nonadherence										
22	I ask patients about their views of whether they need their medication or not, which may have resulted in nonadherence										
23	I ask patients if there are practical reasons (e.g., poor memory, difficulty opening medication bottles) which make it difficult for them to take their medication as prescribed										
24	I discuss with patients what form of support they would like to help them take their medications as prescribed										
25	When patients have difficulty taking their medications as prescribed I suggest solutions which address the specific problems they are having										
26	I offer patients skill building support to increase the patients capacity to deal with practical aspects of medication taking (e.g. how to administer injectable drug)										

27	I review treatment goals with patients and incorporate medication adherence into the review										
28	I encourage involvement of patients in their own care through self-monitoring (e.g.recording glucose levels by people with diabetes)										
29	I use reinforcement to support patients to continue to take their medication e.g. assessment of adherence with patient feedback										
30	I discuss any options available for reducing the cost of the prescription for the patient										
31	I offer rewards for improved adherence and/or treatment response (e.g. reduced frequency of visits; partial payment for equipment)										
32	I use a motivational style (such as motivational interviewing) when discussing medication taking with patients										
33	I use a cognitive-behavioural style when discussing medication taking with patients										
34	I use an educational style when discussing medication taking with patients										
35	I schedule more frequent appointments when patients have problems with medication adherence										

<<PREVIOUS<< >>NEXT>>

Screen 7d: Your use of adherence enhancing interventions (continued)

		Do you use this intervention?						If used, in your opinion, is this intervention effective?			
		Never	Occasionally	Sometimes	Frequently	All the time	Not applicable	Not at all	Somewhat	Extremely	Don't know
	Practical strategies to make medication taking easier										
36	I recommend the medication regimen is simplified by reducing administration frequency (e.g. by use of long acting drugs)										
37	I recommend the medication regimen is simplified by the use of combination drugs										
38	I recommend the medication regimen is simplified by reducing the use of multiple medication for a single condition										
39	I recommend the use of the medication formulation most appropriate for each patient (e.g. oral tablet, oral solution, IV injection, patch)										
40	I recommend the use of medication in packaging patients will find easy to use										
41	I help patients to tailor their medication regimen to their own lifestyle										
42	I help patients to use cueing (taking medication in combination with routine behaviours, such as meals, television programs, brushing teeth in the morning)										
43	I recommend reminder systems to patients such as pagers, mobile phone, alarm watches, telephone services, calendars										
44	I recommend medication charts and diaries to patients to help them remember and record when they have taken their medication										
45	I recommend dispensers for organising										

	medication, e.g. pillboxes, monitored dosage systems										
46	I form adherence contracts with patients that describe what the patient, carers and healthcare professionals will do to support the patient's medication adherence										
	Involving others, and other services, to support adherence										
47	I encourage involvement of family or carers in strategies and interventions for medication adherence										
48	I arrange medication counselling by a specialist for patients to support medication adherence										
49	I refer patients to peer mentor programmes to support medication adherence										
50	I refer to case management services for high risk patients to support medication adherence										

<PREVIOUS<< >>NEXT>>

Screen 8: Barriers to your use of adherence enhancing interventions

Please indicate to what extent the items in the list below act as barriers that limit YOUR use of adherence enhancing interventions (Please click only one option in each row).

After answering the questions, go to the next screen by clicking the NEXT button at the bottom.

	Do the following act as barriers to your use of adherence enhancing interventions?	Not at all	Slightly	Moderately	Very much	Not applicable
1	I find it difficult identifying nonadherence in my patients					
2	I lack experience in the use of adherence management practices					
3	I have limited access to evidence-based information about which adherence enhancing interventions are beneficial under what circumstances					
4	I had no or limited opportunity to study adherence management during pre-qualification training					
5	I have no or limited opportunity to study adherence management post qualification					
6	I lack training in managing long-term conditions					
7	Lack of a co-ordinated approach by all the healthcare providers involved in a patient's care prevents me from supporting patients with medication adherence					
8	Lack of continuity of patient care prevents me from supporting patients with medication adherence					
9	I have an excessive workload that prevents me from supporting patients with medication adherence					

10	I have short consultation times with patients that prevent me from supporting patients with medication adherence					
11	I have difficulty involving patients in decisions about their medication					
12	There are inadequate resources available in the healthcare system to enable me to support medication adherence					
13	There is a lack of performance based payment incentives to encourage me to support adherence					

<<PREVIOUS<< >>NEXT>>

Screen 9: Questions about training and guidelines

This is the last set of questions in the survey, you are nearly there.
We would like to ask you some questions about any training you may have received and your use of any adherence guidelines that are available to you.
After answering the questions, go to the next screen by clicking the NEXT button at the bottom.

1. Have you had any pre-registration training in medication adherence management and support?

   Yes / No

2. Have you had any post-registration training in medication adherence management and support?

   Yes / No

3. Do you use any practitioner guidelines to assist you to manage patient adherence to medication?

   Yes / No

   3a. If yes, which one do you use?

   ……

<<PREVIOUS<< >>NEXT>>

Screen 10: Thank you

THANK YOU!

We would like to thank you very much for completing this survey.

If you have any questions, please do not hesitate to e-mail us:

ABC@mema.keele.ac.uk

To learn more about the ABC Project, please visit www.ABCproject.eu
Please take time to visit the project website (www.ABCproject.eu) in the spring of 2012 to view the results of the ABC project in general and especially, this survey.
The ABC Project Team

>>SUBMIT>>

Ineligibility screen: Thank you

THANK YOU!

We would like to thank you very much for your interest in participating in this survey. Unfortunately, your responses do not meet the requirements for the target population for this survey. Our target population includes fully qualified and licensed doctors, pharmacists and nurses who work in the community with adults. If you feel that you meet these criteria but have been redirected to this page, or if you have any questions, please do not hesitate to e-mail us:

ABC@mema.keele.ac.uk

We would like to thank you for your willingness to fill out the questionnaire and hope that you will be able to help us on other research projects in the future.

The ABC Project Team

>>SUBMIT>>

Appendix 6.1 Assessment of adherence interventions: specific search combinations used in each database

MEDLINE via Pubmed:

First search:

1. Patient Compliance[Mesh]
2. Treatment Refusal[Mesh]
3. Medication Therapy Management[Mesh]
4. #1 OR #2 OR #3
5. monitor*
6. MEMS
7. eDEM
8. electronic
9. microelectronic
10. #5 OR #6 OR # 7 OR # 8 OR #9
11. interven*
12. feedback
13. improv*
14. #11 OR #12 OR #13
15. #4 AND#10 AND# 14
16. Limits: Publication date from inception to 2010/02/19

Second search:

1. Patient Compliance[Mesh]
2. Treatment Refusal[Mesh]
3. Medication Therapy Management[Mesh]
4. #1 OR #2 OR #3
5. MEMS
6. eDEM
7. electronic
8. microelectronic
9. monitor*
10. device
11. pill bottle
12. inhal*
13. drop
14. blister
15. #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
16. #4 AND #15
17. Limits: Publication date from inception to 2010/02/19

EMBASE

First search:

1. Patient compliance/ exp
2. Treatment refusal/exp
3. #1 OR #2
4. MEMS
5. monitor
6. edem
7. electronic
8. microelectronic
9. #4 OR #5 OR #6 OR #7 OR #8
10. Medication therapy management/ exp
11. Intervention study/ exp
12. Patient counseling/exp
13. #10 OR #11 OR #12
14. Limits: Publication date from inception to 2010/03/16; Humans, embase/lim

Second search:

1. Patient compliance/ exp
2. Treatment refusal/exp
3. #1 OR #2
4. MEMS
5. monitor
6. edem
7. electronic
8. microelectronic
9. #4 OR #5 OR #6 OR #7 OR #8
10. Patient counseling/exp
11. Medication therapy management/ exp
12. #10 OR #11
13. #3 AND #9 AND #12
14. Limits: Publication date from inception to 2010/03/16; Humans, embase/lim

Cinahl EBSCOhost

1. (MH "Medication Compliance")
2. (MH "Treatment Refusal")
3. "medication adherence"
4. (MH "Self Administration")
5. #1 OR #2 OR #3 OR #4
6. monitor*
7. MEMS
8. eDEM
9. electronic*
10. microelectronic*
11. #6 OR #7 OR #8 OR #9 OR #10
12. interven*
13. feedback
14. improv*
15. #12 OR #13 OR #14
16. #5 AND #11 AND #15
17. Limits : Publication date from inception to 2010/04/15

PsycINFO

1. adheren*
2. nonadheren*
3. non-adheren*
4. complian*
5. noncomplian*
6. non-complian*
7. 1 or 2 or 3 or 4 or 5 or 6
8. monitor*
9. MEMS
10. eDEM
11. electronic*
12. microelectronic*
13. 8 or 9 or 10 or 11 or 12
14. interven*
15. feedback
16. improv*
17. 14 or 15 or 16
18. 7 and 13 and 17
19. Limits : Publication date from inception to 2010/04/15

The Cochrane Library

1. MeSH descriptor Patient Compliance explode all trees

2. MeSH descriptor Treatment Refusal explode all trees
3. MeSH descriptor Medication Therapy Management explode all trees
4. MeSH descriptor Electronics, Medical explode all trees
5. (monitor*)
6. (MEMS)
7. (eDEM)
8. (electronic*)
9. (microelectronic*)
10. (interven*) or (feedback) or (improv*)
11. ((#4 OR #5 OR #6 OR #7 OR #8 OR #9) AND #10)
12. (#1 OR #2 OR #3)
13. (#12 AND #11)
14. Limits : Publication date from inception to 2010/04/28

Appendix 6.2 Assessment of adherence interventions: study characteristics and results

CG: control group
INT: intervention group
NR: not reported
Rewards: any kind of rewards
Tech equip: Interventions based on a technical equipment use
Tech rem: Interventions based on a technical reminder use
EM-feedback: Interventions based on EM-adherence feedback
Soc-Psych: Social – Psycho-affective interventions
Behav-Counsel : Behavioral – Counseling interventions
Cogn-Educ: Cognitive – Educational interventions
TRT simpl: Intervention based on treatment simplification

References	Disease	Participant characteristics	Gender	# participants analyzed	Intervention components	Intervention description	Duration of follow-up (entire patient follow up period)	Duration of intervention (1st int-last int)	Occupation of the person delivering the intervention	Effect on Clinical Outcome (YES/NO)
Andrade *et al.* 2005 [55]	HIV	*Mean Age* CG: 38.0 INT: 38.0	*% female* CG: 38.0 INT: 45.0	CG: 29 INT: 29	Tech rem	Voice message reminder	24 weeks	24 weeks	NR	NO
Andrejak *et al.* 2000 [56]	Hypertension	*Mean Age* CG: 59.0 INT: 55.0	*% female* CG: 53.0 INT: 56.0	CG: 62 INT: 71	TRT simpl	Regimen simplification (QD vs BID)	26 weeks	26 weeks	NR	NO
Berg *et al.* 1997 [57]	Asthma	*Mean Age* CG: 52.0 INT: 47.0	*% female* CG: 62.0 INT: 68.0	CG: 24 INT: 31	Cogn-Educ Behav-Counsel Tech equip	6 self-management education sessions and self-monitoring of peak flow rates and symptoms	8 weeks	6 weeks	Nurse	NO
Berkovitch *et al.* 1998 [58]	Sickle cells disease	*Mean Age* CG: NR INT: NR	*% female* CG: NR INT:NR	CG: 6 INT: 7	Cogn-Educ Behav-Counsel Soc-Psych	Educational slideshow; stickers and calendar as a self-monitoring diary; weekly follow-up telephone calls	24 weeks	8 weeks	Social worker	NO
Bogner & de Vries 2008 [32]	Hypertension	*Mean Age* CG: 57.5 INT: 59.7	*% female* CG: 78.1 INT: 75.0	CG: 32 INT: 32	Cogn-Educ	3, in-person sessions and 2 telephone contacts	6 weeks	6 weeks	Integrated care manager	YES
Bouvy *et al.* 2003 [59]	Heart Failure	*Mean Age* CG: 70.2 INT: 69.1	*% female* CG: 53.0 INT: 47.0	CG: 43 INT: 48	EM-feedback	EM-feedback	26 weeks	26 weeks	Pharmacist	NO
Boyle *et al.* 2008 [60]	HIV	*Mean Age* CG: 42.1 INT: 42.3	*% female* CG: 25.3 INT: 19	CG: 80 INT: 171	TRT simpl	Regimen simplification (QD vs BID)	48 weeks	48 weeks	NR	NO
Brook *et al.* 2005 [61]	Depression	*Mean Age* CG: NR INT: NR	*% female* CG: NR INT: NR	CG: 71 INT: 64	Cogn-Educ Behav-Counsel	Video emphasizing the importance of adherence, and 3 coaching sessions	26 weeks	26 weeks	Pharmacist	NO

References	Disease	Participant characteristics	Gender	# participants analyzed	Intervention components	Intervention description	Duration of follow-up (entire patient follow up period)	Duration of intervention (1st int-last int)	Occupation of the person delivering the intervention	Effect on Clinical Outcome (YES/NO)
Brown, *et al.* 2009 [36]	Epilepsy	*Mean Age* CG: 44.1 INT: 41.9	*% female* CG: 62.0 INT: 58.0	CG: 32 INT: 37	Behav-Counsel	Self administered work-sheet where the subject writes and reads back to him or her-self their intention to adhere and their plan for how to follow their regimen	4 weeks	0 weeks (intervention applied once)	NR	NR
Burgess *et al.* 2007 [62]	Asthma	*Mean Age* CG: 3.8 INT: 3.4	*% female* CG: 38.0 INT: 31.0	CG: 20 INT: 24	Rewards	MDI spacer with incentive toy	12 weeks	12 weeks	Support partner	NO
Burgess *et al.* 2010 [63]	Asthma	*Mean Age* CG: 9.3 INT: 9.1	*% female* CG: 42.0 INT: 21.0	CG: 12 INT: 14	EM-feedback	EM-feedback	16 weeks	16 weeks	Physician Nurse Support partner	NR
Charles *et al.* 2007 [64]	Asthma	*Mean Age* CG: 35.0 INT: 39.0	*% female* CG: 60.0 INT: 49.0	CG: 46 INT: 44	Tech rem	MDI device with audiovisual adherence reminder function	24 weeks	24 weeks	NR	NO
Clowes *et al.* 2004 [21]	Osteoporosis	*Mean Age* CG: 61.8 INT 1: 64.1 INT 2: 61.2	*% female* CG: 100 INT 1&2: 100	CG: 24 INT1: 25 INT2: 24	Behav-Counsel Tech equip	INT 1: Nurse monitoring with predefined interview INT 2: Marker monitoring: feedback on biomarker	48 weeks	48 weeks	Nurse	NR
Cramer & Rosenheck 1999 [65]	Psychotic disorders	*Mean Age* CG: 48.0 INT: 46.0	*% female* CG: 12.0 INT: 15.0	CG: 20 INT: 25	Behav-Counsel EM-feedback	Medication Usage Skills for Effectiveness (MUSE), feedback on adherence data	26 weeks	26 weeks	Research assistant	NR
De Geest *et al.* 2006 [66]	Transplantation	*Mean Age* CG: NR INT: NR	*% female* CG: NR INT: NR	CG: 9 INT: 4	TRT simpl Cogn-Educ Behav-Counsel Soc-Psych EM-feedback Tech rem	Adherence counseling, self-efficacy interventions, EM- feedback, medication education; cueing; reminders/stimuli; possibly regimen simplification; social support suggestions; telephone follow-up for 3 months	36 weeks	12 weeks	Nurse	NR

References	Disease	Participant characteristics	Gender	# participants analyzed	Intervention components	Intervention description	Duration of follow-up (entire patient follow up period)	Duration of intervention (1st int-last int)	Occupation of the person delivering the intervention	Effect on Clinical Outcome (YES/NO)
Delmas *et al.* 2007 [25]	Osteoporosis	*Mean Age* CG: 71.5 INT: 71.1	*% female* CG: 100 INT: 100	CG: 1113 INT: 1189	Behav-Counsel Tech equip	Feedback on biomarker Steps intended to remind the patients to take the medication (e.g. linking intake of medication to patient's habits like brushing teeth)	52 weeks	39 weeks	Physician	NR
Dilorio *et al.* 2008 [67]	HIV	*Mean Age* CG: 41.0 INT: 41.0	*% female* CG: 32.0 INT: 34.0	CG: 106 INT: 107	Behav-Counsel	Motivational interviewing	52 weeks	12 weeks	Nurse	NO
Düsing *et al.* 2009 [26]	Hypertension	*Mean Age* CG: 52.8 INT: 49.8	*% female* CG: 45.7 INT: 45.4	CG: 97 INT: 94	Cogn-Educ Behav-Counsel Soc-Psych Tech rem Tech equip	24h timer with an acoustic signal; set of reminding stickers, information brochure, information letter for family member, home BP measurement	38 weeks	34 weeks	Physician	NO
Frick *et al.* 2001 [40]	HIV (vitamin therapy)	*Mean Age* CG: 26.0 INT: 26.0	*% female* CG: 100 INT: 100	CG: 59 INT: 61	Tech rem	Medication vials with alarm reminder feature	4 weeks	4 weeks	NR	NR
Fulmer *et al.* 1999 [22]	Congestive heart failure	*Mean Age* CG: 73.7 INT 1: 76.2 INT 2: 73.1	*% female* CG: NR INT 1&2: NR	CG: 14 INT1: 13 INT2: 15	Tech rem	INT 1: daily telephone call reminder INT 2: daily videotelephone call reminder	10 weeks	6 weeks	Research assistant	NR
Grosset & Grosset 2007 [33]	Parkinson	*Mean Age* CG: 66.0 INT: 61.0	*% female* CG: 49.0 INT: 38.0	CG: 29 INT: 23	Cogn-Educ	Verbal and written education	24 weeks	0 weeks (intervention applied once)	Investigator	NO

References	Disease	Participant characteristics	Gender	# participants analyzed	Intervention components	Intervention description	Duration of follow-up (entire patient follow up period)	Duration of intervention (1st int-last int)	Occupation of the person delivering the intervention	Effect on Clinical Outcome (YES/NO)
Holzemer *et al.* 2006 [68]	HIV	*Mean Age* CG: NR INT: NR	*% female* CG: NR INT: NR	CG: 89 INT: 91	TRT simpl Cogn-Educ Behav-Counsel	CAP-IT which included items related to knowledge, reasons for missed doses, memory aids, side effects, medication troubles, and patient-provider relationship	26 weeks	26 weeks	Nurse	NR
Hyder *et al.* 2002 [27]	Prenatal iron supplementation	*Mean Age* CG: NR INT: NR	*% female* CG: 100 INT: 100	CG: 85 INT: 86	TRT simpl	Regimen simplification (QD vs weekly)	7 weeks	7 weeks	NR	NR
Janson *et al.* 2003 [69]	Asthma	*Mean Age* CG: 35.0 INT: 32.0	*% female* CG: 56.0 INT: 55.0	CG: 32 INT: 33	Cogn-Educ Behav-Counsel Tech equip	Written asthma action plan, asthma & medication education, Peak flow feedback	6 weeks	7 weeks	Nurse	NO
Janson *et al.* 2009 [70]	Asthma	*Mean Age* CG: 39.7 INT: 36.8	*% female* CG: 54.0 INT: 53.0	CG: NR INT: NR	Cogn-Educ Behav-Counsel Tech equip	Asthma & medication education, Peak flow feedback	22 weeks	4 weeks	Nurse Respiratory therapist	NO
Kardas 2005 [44]	Diabetes	*Mean Age* CG: 62.4 INT: 60.9	*% female* CG: 62.0 INT: 47.0	CG: 50 INT: 50	TRT simpl	Regimen simplification (QD vs BID)	16 weeks	16 weeks	NR	YES
Kardas 2007 [71]	Angina pectoris	*Mean Age* CG: 55.0 INT: 58.5	*% female* CG: 53.1 INT: 66.0	CG: 49 INT: 47	TRT simpl	Regimen simplification [QD vs BID)	8 weeks	8 weeks	NR	NO
Kardas 2004 [43]	Angina pectoris	*Mean Age* CG: NR INT: NR	*% female* CG: NR INT: NR	CG: 48 INT: 49	TRT simpl	Regimen simplification (QD vs BID)	8 weeks	8 weeks	NR	YES
Klein *et al.* 2009 [34]	Transplantation	*Mean Age* CG: 50.1 INT: 52.8	*% female* CG: 46.0 INT: 46.0	CG: 21 INT: 20	TRT simpl Cogn-Educ	Medication education, laboratory values, drug-related problems, simplifying the drug regimen	52 weeks	52 weeks	Pharmacist Support partner	NR
Koenig *et*	HIV	*Mean Age*	*% female*	CG: 116	Cogn-Educ	Structured needs	26 weeks	26 weeks	Nurse	NO

References	Disease	Participant characteristics	Gender	# participants analyzed	Intervention components	Intervention description	Duration of follow-up (entire patient follow up period)	Duration of intervention (1st int-last int)	Occupation of the person delivering the intervention	Effect on Clinical Outcome (YES/NO)
***al.* 2008** [72]		CG: 37.0 INT: 37.0	CG: 34.0 INT: 39.0	INT: 110	Behav-Counsel Soc-Psych	assessment, medication education, support partners involved, phone contacts				
Kozuki & Schepp 2006 [73]	Psychotic disorders	*Mean Age* CG: NR INT: NR	*% female* CG: NR INT: NR	CG: 14 INT: 15	Behav-Counsel EM-feedback	Psychodynamic counseling to improve Behav-Counsel insights, EM-feedback	12 weeks	12 weeks	Research therapist	NO
Leenen *et al.* 1997 [74]	Hypertension	*Mean Age* CG: 55.0 INT: 55.0	*% female* CG: 40.0 INT: 37.0	CG: 85 INT: 105	TRT simpl	Regimen simplification (QD vs BID)	24 weeks	20 weeks	Physician Nurse	NR
Maitland *et al.* 2008 [75]	HIV	*Mean Age* CG:47.1 [median] INT:46.5[median]	*% female* CG: 8.5.0 INT: 8.5.0	CG: 47 INT: 47	TRT simpl	Regimen simplification (QD vs BID)	8 weeks	4 weeks	NR	NO
Marquez-Contreras *et al.* 2006 [76]	Hypertension	*Mean Age* CG: 58.9 INT: 59.3	*% female* CG: 50.0 INT: 48.0	CG: 100 INT: 100	Tech equip	Home blood pressure monitoring programme (OMRON)	24 weeks	24 weeks	NR	NO
Mooney *et al.* 2007 [77]	Smoking cessation	*Mean Age* CG: NR INT: NR	*% female* CG: 100 INT: 100	CG: NR INT: NR	Cogn-Educ Behav-Counsel EM-feedback	Cognitive behavioral therapy sessions EM-feedback	6 weeks	6 weeks	Therapist	NO
Mounier-Vehier *et al.* 1998 [78]	Hypertension	*Mean Age* CG: 55.5 INT: 54.2	*% female* CG: 55.3 INT: 49.1	CG: 34 INT: 50	TRT simpl	Regimen simplification (QD vs BID)	12 weeks	12 weeks	Physician	NO
Murray *et al.* 2007 [41]	Heart Failure	*Mean Age* CG: 62.6 INT: 61.4	*% female* CG: 66.1 INT: 68.0	CG: 192 INT: 122	Cogn-Educ Behav-Counsel	Pharmacist-delivered protocol including medication education, written instructions, communication with patients' health care providers	52 weeks	36 weeks	Pharmacist	NO
Ogedegbe	Hypertension	*Mean Age*	*% female*	CG: 81	Behav-Counsel	Motivational interviewing	52 weeks	36 weeks	Research	NO

References	Disease	Participant characteristics	Gender	# participants analyzed	Intervention components	Intervention description	Duration of follow-up (entire patient follow up period)	Duration of intervention (1st int-last int)	Occupation of the person delivering the intervention	Effect on Clinical Outcome (YES/NO)
***et al.* 2008** [79]		CG: 54.0 INT: 53.5	CG: 50.0 INT: 50.0	INT: 79					assistant	
Okeke *et al.* 2009 [80]	Glaucoma	*Mean Age* CG: 63.8 INT: 66.2	*% female* CG: 41.9 INT: 48.6	CG: 31 INT: 35	Cogn-Educ Behav-Counsel Tech rem	Educational video, adherence counseling with study coordinator, medication calendar diary, and barriers counseling, reminder telephone	24 weeks	12 weeks	Coordinator	NO
Ollivier *et al.* 2009 [42]	Malaria prophylaxis	*Mean Age* CG: NR INT: NR	*% female* CG: NR INT: NR	CG: 187 INT: 148	Tech rem	Daily text-message reminder	4 weeks	4 weeks	NR	NR
Onyirimba *et al.* 2003 [81]	Asthma	*Mean Age* CG: 53.0 INT: 45.0	*% female* CG: 78.0 INT: 90.0	CG: 9 INT: 10	Cogn-Educ Behav-Counsel EM-feedback Tech equip	EM-feedback discussion of strategies to improve adherence	10 weeks	3 weeks	Physician Nurse Respiratory therapist	NO
Parienti *et al.* 2007 [82]	HIV	*Mean Age* CG: NR INT: NR	*% female* CG: NR INT: NR	CG: 25 INT: 27	TRT simpl	Regimen simplification (QD vs BID)	52 weeks	16 weeks	NR	NR
Portsmouth *et al.* 2005 [83]	HIV	*Mean Age* CG: 45.0 INT: 40.0	*% female* CG: 14.0 INT: 4.5	CG: 18 INT: 20	TRT simpl	Regimen simplification (QD vs BID)	24 weeks	24 weeks	NR	NO
Qureshi *et al.* 2007 [28]	Hypertension	*Mean Age* CG: 54.4 INT: 56.6	*% female* CG: 61.0 INT: 64.0	CG: 97 INT: 81	Cogn-Educ	1-day intensive training session for general practitioners on pharmacological and non-pharmacological interventions, use of lower-cost and single-dose drug regimens, scheduled follow-up visits, etc.	6 weeks	6 weeks	Physician Community health worker	NR
Rapoff *et al.* 2002 [84]	Juvenile Rheumatoid Arthritis	*Mean Age* CG: 8.2 INT: 8.6	*% female* CG: 73.0 INT:63.0	CG: 15 INT: 19	Cogn-Educ Behav-Counsel Soc-Psych	Educational & Behav-Counsel intervention, audiovisual program and booklet, follow-up phone	56 weeks	52 weeks	Nurse	NO

References	Disease	Participant characteristics	Gender	# participants analyzed	Intervention components	Intervention description	Duration of follow-up (entire patient follow up period)	Duration of intervention (1st int-last int)	Occupation of the person delivering the intervention	Effect on Clinical Outcome (YES/NO)
						contacts				
Rathbun *et al.* 2005 [38]	HIV	*Mean Age* CG: 38 [median] INT: 38 [median]	*% female* CG: 75.0 INT: 25.0	CG: 17 INT: 16	Cogn-Educ Behav-Counsel Tech rem	Education, monitoring of progress, visual aids and reminder devices	28 weeks	28 weeks	Pharmacist	NO
Rawlings *et al.* 2003 [85]	HIV	*Mean Age* CG: 37.7 INT: 35.7	*% female* CG: 31.0 INT: 39.0	CG: 76 INT: 65	Cogn-Educ Behav-Counsel	Small-group educational sessions, flip charts, videotapes, patient logbooks, and patient workbooks	24 weeks	24 weeks	Health care professional	NO
Remien *et al.* 2005 [86]	HIV	*Mean Age* CG: NR INT: NR	*% female* CG: NR INT: NR	CG: 94 INT: 88	Cogn-Educ Behav-Counsel Soc-Psych	Counseling sessions with patient & partner, education about importance of adherence	32 weeks	32 weeks	Nurse	NO
Rigsby *et al.* 2000 [23]	HIV	*Mean Age* CG: 47.2 INT 1: 44.6 INT 2: 43.9	*% female* CG: 0 INT 1: 14.0 INT 2: 20.0	CG: NR INT1: NR INT2: NR	INT1: Behav-Counsel EM-feedback INT2: Behav-Counsel EM-feedback Rewards	INT 1: cue-dose training, EM- feedback INT 2: cue-dose training, EM- feedback, cash monetary reinforcement for good adherence	12 weeks	4 weeks	Research assistant without medical training	NO
Rosen *et al.* 2004 [39]	Diabetes	*Mean Age* CG: 63.5 INT: 62.3	*% female* CG: NR INT: NR	CG: 17 INT: 16	Behav-Counsel EM-feedback Tech rem	Electronic monitor with reminder, EM-feedback	16 weeks	28 weeks	Bachelor research assistant	NO
Rudd *et al.* 2004 [45]	Hypertension	*Mean Age* CG: 60.0 INT: 59.0	*% female* CG: 56.0 INT: 50.0	CG: 68 INT: 69	TRT simpl Cogn-Educ Tech equip	Home BP measurement, side effects education, and follow-up phone contacts	24 weeks	24 weeks	Nurse	YES
Safren *et al.* 2003 [30]	HIV	*Mean Age* CG: NR INT: NR	*% female* CG: NR INT: NR	CG: 25 INT: 19	Tech rem	Reminders send to pagers	12 weeks	10 weeks	NR	NR
Safren *et al.* 2009 [87]	HIV	*Mean Age* CG: NR INT: NR	*% female* CG: NR INT: NR	CG: 17 INT: 19	Cogn-Educ Behav-Counsel EM-feedback	Cognitive Behav-Counsel therapy to address strategies for and barriers	52 weeks	12 weeks	Psychologist	NR

References	Disease	Participant characteristics	Gender	# participants analyzed	Intervention components	Intervention description	Duration of follow-up (entire patient follow up period)	Duration of intervention (1st int-last int)	Occupation of the person delivering the intervention	Effect on Clinical Outcome (YES/NO)
					Tech rem	to medication adherence; EM-feedback				
Schmitz *et al.* 2005 [88]	Smoking cessation	*Mean Age* CG: 48.1 INT: 48.9	*% female* CG: 100 INT: 100	CG: NR INT: NR	EM-feedback	EM-feedback	7 weeks	7 weeks	Nurse	NR
Simoni *et al.* 2007 [89]	HIV	*Mean Age* CG: 42.5 INT: 42.6	*% female* CG: 38.5 INT: 50.7	CG: 57 INT: 59	Soc-Psych	Peer support through meetings & phone calls	24 weeks	12 weeks	Peer led social support	NO
Simoni *et al.* 2009 [24]	HIV	*Mean Age* CG: NR INT 1&2&3: NR	*% female* CG: NR INT 1&2&3: NR	CG: 57 INT1: 57 INT2: 56 INT3: 54	INT1: Behav-Counsel Soc-Psych INT2: Cogn-Educ Tech rem INT3: Cogn-Educ Behav-Counsel Soc-Psych Tech rem	INT 1 : peer support through meetings & phone calls INT 2: Pager reminder INT 3: INT 1 & INT 2	36 weeks	12 weeks	INT1 : Support partner INT2 : NR INT3 : Support partner	NO
Smith *et al.* 2003 [90]	HIV	*Mean Age* CG: NR INT: NR	*% female* CG: 12.0 INT: 7.0	CG: 9 INT: 8	Cogn-Educ Behav-Counsel Soc-Psych EM-feedback	Adherence counseling, self-monitoring, goal-setting, enlistment of self-incentives for adherence, and enlisting social support	12 weeks	12 weeks	Nurse Pharmacist	NO
Sorensen *et al.* 2007 [91]	HIV	*Mean Age* CG: 42.6 INT: 44.0	*% female* CG: 47.0 INT: 35.0	CG: 26 INT: 31	Behav-Counsel EM-feedback	Medication coaching sessions plus voucher reinforcement for goods and services in the community	20 weeks	12 weeks	Nurse Research assistant	NO
Udelson *et al.* 2009 [92]	Heart Failure	*Mean Age* CG: 65.5 INT: 65.1	*% female* CG: 29.0 INT: 23.5	CG: 131 INT: 135	TRT simpl	Regimen simplification (QD vs BID)	20 weeks	20 weeks	Nurse	NO
Vrijens *et al.* 2006 [29]	Hypercholesterolemia	*Mean Age* CG: 60.4	*% female* CG: 54.0	CG: 198 INT: 194	Cogn-Educ EM-feedback	EM-feedback, information sheet about disease, risk	52 weeks	52 weeks	Pharmacist	NR

References	Disease	Participant characteristics	Gender	# participants analyzed	Intervention components	Intervention description	Duration of follow-up (entire patient follow up period)	Duration of intervention (1st int-last int)	Occupation of the person delivering the intervention	Effect on Clinical Outcome (YES/NO)
		INT: 62.9	INT: 45.0		Tech rem	factors, dietary information, beep-card reminder				
Wagner *et al.* 2006 [93]	HIV	*Mean Age* CG: NR INT: NR	*% female* CG: NR INT: NR	CG: 52 INT: 96	Cogn-Educ Behav-Counsel EM-feedback	Cognitive Behav-Counsel intervention, EM feedback	48 weeks	48 weeks	Nurse	NO
Wall *et al.* 1995 [94]	HIV	*Mean Age* CG: NR INT: NR	*% female* CG: NR INT: NR	CG: 12 INT: 13	Behav-Counsel Tech equip	DOT Monday through Friday, feedback on biomarkers	12 weeks	8 weeks	Nurse	NO
Weber *et al.* 2004 [35]	HIV	*Mean Age* CG: 40.2 INT: 41.5	*% female* CG: 7.1 INT: 25.0	CG: 24 INT: 29	Behav-Counsel EM-feedback	Cognitive Behav-Counsel therapy, goal-setting	52 weeks	52 weeks	Physician Nurse Psychologist	NO
Williams *et al.* 2006 [37]	HIV	*Mean Age* CG: NR INT: NR	*% female* CG: 52.0 INT: 45.0	CG: 40 INT: 47	Cogn-Educ Behav-Counsel Soc-Psych	Educational intervention delivered during home visits	64 weeks	52 weeks	Nurse Community health worker	NO
Wilson *et al.* 2010 [31]	HIV	*Mean Age* CG: NR INT: NR	*% female* CG: NR INT: NR	CG: NR INT: NR	EM-feedback	Provider was given a report prior to clinic visit including data on self-reported adherence, EM adherence, reminder use, beliefs about ART, reasons for missed doses, alcohol & drug use, and depression	NR	NR	Physician	NR

Appendix 7.1 Health economics literature search strategies for electronic databases

MEDLINE (Ovid)

1. patient compliance [Majr]
2. treatment Refusal [Majr]
3. #1 OR #2

AND

1. economics/
2. exp "costs and cost analysis"/
3. economics, dental/
4. exp "economics, hospital"/
5. economics, medical/
6. economics, nursing/
7. economics, pharmaceutical/
8. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
9. (expenditure$ not energy).ti,ab.
10. (value adj1 money).ti,ab.
11. budget$.ti,ab.
12. or/1-11
13. ((energy or oxygen) adj cost).ti,ab.
14. (metabolic adj cost).ti,ab.
15. ((energy or oxygen) adj expenditure).ti,ab.
16. or/13-15
17. 12 not 16
18. letter.pt.
19. editorial.pt.
20. historical article.pt.
21. or/18-20
22. 17 not 21
23. Animals/
24. Humans/
25. 23 not (23 and 24)
26. 22 not 25

CINAHL (EBSCO)

1. adherence
2. compliance
3. persistence
4. concordance

5. nonadherence
6. non-adherence
7. noncompliance
8. non-compliance
9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

AND

1. MH "Economics+"
2. MH "Financial Management+"
3. MH "Financial Support+"
4. MH "Financing, Organized+"
5. MH "Business+"
6. S2 OR S3 or S4 OR S5
7. S1 NOT S6
8. MH "Health Resource Allocation"
9. MH "Health Resource Utilization"
10. S8 OR S9
11. S7 OR S10
12. TI (cost or costs or economic* or pharmacoeconomic* or price* or pricing*) OR AB (cost or costs or economic* or pharmacoeconomic* or price* or pricing*)
13. S11 OR S12
14. PT editorial
15. PT letter
16. PT commentary
17. S14 or S15 or S16
18. S13 NOT S17
19. MH "Animal Studies"

EMBASE (Ovid)

1. patient compliance/exp/mj
2. pharmaceutic*
3. prescript*
4. medicat*
5. medicament
6. medicine
7. medicines
8. drug
9. drugs
10. #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

AND

1. health-economics/

2. exp economic-evaluation/
3. exp health-care-cost/
4. exp pharmacoeconomics/
5. 1 or 2 or 3 or 4
6. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab
7. (expenditure$ not energy).ti,ab
8. (value adj2 money).ti,ab
9. budget$.ti,ab
10. 6 or 7 or 8 or 9
11. 5 or 10
12. letter.pt
13. editorial.pt
14. note.pt
15. 12 or 13 or 14
16. 11 not 15
17. (metabolic adj cost).ti,ab
18. ((energy or oxygen) adj cost).ti,ab
19. ((energy or oxygen) near expenditure).ti,ab
20. 17 or 18 or 19
21. 16 not 20
22. exp animal/
23. exp animal-experiment/
24. nonhuman/
25. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh
26. 22 or 23 or 24 or 25
27. exp human/
28. exp human-experiment/
29. 27 or 28
30. 26 not (26 and 29)
31. 21 not 30

PsychINFO

1. compliance
2. adherence
3. concordance
4. persistence
5. noncomplicance
6. non-compliance
7. nonadherence
8. non-adherence
9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

AND

1. "costs and cost analysis"/
2. "Cost Containment"/
3. (economic adj2 evaluation$).ti,ab.
4. (economic adj2 analy$).ti,ab.
5. (economic adj2 (study or studies)).ti,ab.
6. (cost adj2 evaluation$).ti,ab.
7. (cost adj2 analy$).ti,ab.
8. (cost adj2 (study or studies)).ti,ab.
9. (cost adj2 effective$).ti,ab.
10. (cost adj2 benefit$).ti,ab.
11. (cost adj2 utili$).ti,ab.
12. (cost adj2 minimi$).ti,ab.
13. (cost adj2 consequence$).ti,ab.
14. (cost adj2 comparison$).ti,ab.
15. (cost adj2 identificat$).ti,ab.
16. (pharmacoeconomic$ or pharmaco-economic$).ti,ab.
17. or/1-16
18. (task adj2 cost$).ti,ab,id.
19. (switch$ adj2 cost$).ti,ab,id.
20. (metabolic adj cost).ti,ab,id.
21. ((energy or oxygen) adj cost).ti,ab,id.
22. ((energy or oxygen) adj expenditure).ti,ab,id.
23. or/18-22
24. (animal or animals or rat or rats or mouse or mice or hamster or hamsters or dog or dogs or cat or cats or bovine or sheep or ovine or pig or pigs).ab,ti,id,de.
25. editorial.dt.
26. letter.dt.
27. dissertation abstract.pt.
28. or/24-27

17 not (23 or 28)

Appendix 7.2 Medication adherence and persistence tool for assessment of RCTs (Gwardry-Sridhar et al. (2009) (23)

Criteria	Urien (2004) (24)	Segador (2005) (25)	Comments
Was a power calculation performed a priori to determine sample size?	1	1	
Were the inclusion and exclusion criteria for patients clearly defined?	1	1	
Was methods of randomization or allocation reported	0	1	
If randomisation was reported, was an appropriate method of randomisation used?	0	1	
Were the patients blinded to the randomization?	1	0	
Were the outcome assessors blinded to the treatment received?	0	1	Analysis blind
Were there intervention and usual care groups assigned?	0	1	No mention of usual care in either paper. Both had control groups - Segador verbal information only, intervention group also had written information; Urien "thorough educational advice by detailed and appropriate verbal instructions.....and carefully taught how to comply with treatment" intervention group as control plus phone call
Was the therapeutic regimen for the usual care group explicitly explained?	1	1	
Was the therapeutic regimen for the intervention group explicitly explained?	1	1	
Was there identification of whether adherence was a primary or secondary outcome?	1	1	

Criteria	Urien (2004) (24)	Segador (2005) (25)	Comments
Was there an explicitly stated adherence measure?	1	1	
Was the choice of adherence measure justified?	1	1	
Were the criteria used for measuring outcomes objective?	1	1	
Were the adherence results reported according to the measure that was selected?	1	1	
Were there explicitly stated outcome measures and reported results?	1	1	
Was the follow-up period of sufficient length for the disease group being studied?	1	1	
Was an appropriate statistical data analysis carried out?	1	1	
If this was a longitudinal study. Were temporal relations considered?	NA	NA	
If the study produced a negative result, were confidence intervals or post hoc power calculations performed?	NA	NA	
Do you know how many patients were excluded from the trial?	0	0	
Was there a description of withdrawals and dropouts?	1	1	Segador had none
Was a table provided for the withdrawals and dropouts?	0	1	
Score obtained in relation to maximum score (2 not applicable max score = 20)	14	18	

Appendix 7.3 JADAD critical appraisal criterion (22)

JADAD Critical Appraisal Criterion	Assessment of Urien 2004	Assessment of Segador 2005
How was allocation concealed?	There was no description of any allocation concealment.	Numbered containers were used to implement the random allocation sequence.
What randomisation technique was used?	The randomisation technique is not described.	A computer generated randomisation sequence with no restrictions.
Was a justification of the sample size provided?	Planned enrolment, allowing for 12% losses, was 128 patients. This number was met, and losses were lower than allowed for by this calculation.	A total of 152 patients were required. This number was exceeded.
Was follow-up adequate?	7 patients (5.5%) were lost to follow-up. 2 patients were excluded because of lack of phone. Reasons for the other losses are not given.	All patients appear to have been followed up.
Were the individuals undertaking the outcomes assessment aware of allocation?	Patients were not told the subject of the study or what group they were allocated to. The researcher was blinded to treatment until after delivering the verbal instructions since these were the same for both arms.	No attempt at blinding was made, due to the nature of the intervention. However the statistical analysis was carried out by a researcher who did not know to which group patients were allocated.
Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.	Parallel-group.	Parallel-group.
Where was the RCT conducted?	This single-centre study was conducted in Spain.	This was a multi-centre study conducted in Spain.
How do the participants included in the RCT compare with patients who are likely to receive the intervention?	Patients were required to have a diagnosis of tonsillitis/pharyngitis of possible bacterial aetiology and to have a phone. Patients with mental illness, or belonging to any group the doctor believed would make them difficult to monitor, were excluded. Information on the patient characteristics is limited. The average age was 32.95. 60.3% were women, 7.4% lived alone and 77.7% did not usually take any other drugs.	Patients had presented to their GP with sore throats that required antibiotic treatment. Patients were required to be literate and able to understand the written instructions. Mental or social problems that might prevent a patient from adhering to treatment were not allowed. The mean age was 47.1 and 44.3% were male.
For pharmaceuticals, what dosage regimens were used in the RCT?	Patients were prescribed three boxes of amoxicillin, dosed according to weight in 500mg, 750mg, and 1g doses, to be taken every 8 hours for 10 days.	All patients received 250mg of oral penicillin V or G every 6 hours for 10 days. Patients who were allergic to penicillin were treated with the same dose of erythromycin, also for 10

JADAD Critical Appraisal Criterion	Assessment of Urien 2004	Assessment of Segador 2005
		days. This prescription required two boxes of tablets, which would leave a surplus of eight pills.
For interventions to improve compliance, was the intervention adequately described?	Patients in the intervention arm were telephoned on the fourth day, when the first box of antibiotics should have been finished. This was expected to be the time when patients would begin to feel better and might be tempted to discontinue treatment. During the call patients were advised to continue treatment as prescribed and reminded that although they may feel better, or even cured, the treatment must be continued for 10 days. Calls were made around lunch or dinner time and messages left if the patient was not in. Patients were called multiple times if necessary.	Patients in the intervention arm received written information at the first visit, with the GP, in addition to the verbal instructions delivered to both groups. The written information emphasised the importance of completing treatment, of respecting the intervals between doses, and the drawbacks of early discontinuation. Patients were asked to read and repeat the instructions out loud in order to test their ability to understand
Were the study groups comparable?	Homogeneity analysis after randomisation did not show any significant differences in age, concomitant drugs for a chronic disease, sex, whether patients lived alone, dose of amoxicillin, occupation or education.	Patients in either arm were comparable in terms of age, sex and antibiotic treatment (penicillin or erythromycin). There were no statistically significant differences between groups for these three characteristics.
Were the statistical analyses used appropriate?	A worst-case scenario analysis was performed alongside an analysis of evaluated patients, assuming all losses from the intervention group were non-compliant, and all losses from the control group were compliant.	The statistical analyses appear to be appropriate.
Was an intention-to-treat analysis undertaken?	The worst-case scenario analysis included all patients.	All analyses were ITT.
How was compliance measured?	Adherence was measured by a spot-check pill-count at the patients' houses on the last, or last but one day of treatment (day 9 or 10). Patients were unaware that their tablets would be counted. Patients were also asked, prior to pill count, "most patients have difficulty in taking their tablets, did you?" After the pill-count, patients were asked about reasons for any non-adherence. The interpretation	A spot-check pill count at the patients home. Patients were told they would be visited at home to check on their clinical progress, but not on which day this would occur. Patients were visited on the 9th to 12th day after commencement of treatment, usually between 14:00 and 15:00, since they were likely to be home at this time. After the pill count patients were asked for reasons for any non-

JADAD Critical Appraisal Criterion	Assessment of Urien 2004	Assessment of Segador 2005
	followed the Canadian criteria for Clinical Epidemiology.	adherence.
Was compliance defined appropriately?	An adherent patient was one who had, according to the pill count, taken 80-110% of the prescribed medication.	An adherent patient was one who had, according to the pill count, taken 80-110% of the prescribed medication.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?		The verbal instructions given to all patients are not detailed.
Score	**Jadad score 2 Allocation Concealment Grade: B (Unclear)**	**Jadad score 3 Allocation Concealment Grade: A**

Appendix 8.1 Health learning outcomes/ competencies relevant to managing patient non-adherence to medications from Tomorrow's Doctors, General Medical Council, UK, http://www.gmc-uk.org/education/undergraduate/tomorrows_doctors.asp

Tomorrow's Doctors - **Outcomes 1 – The doctor as a scholar and a scientist**	
Apply psychological principles, method and knowledge to medical practice	(e) Discuss psychological aspects of behavioural change and treatment compliance
Apply sociological principles, method and knowledge to medical practice	(e) Discuss sociological aspects of behavioural change and treatment compliance
Tomorrow's Doctors- **Outcomes 2 – The doctor as a practitioner**	
The graduate will be able to carry out a consultation with a patient:	(b) Elicit patients' questions, their understanding of their condition and treatment options, and their views
	(f) Determine the extent to which patients want to be involved in decision-making about their care and treatment
Diagnose and manage clinical presentations	(g) Formulate a plan for treatment, management and discharge, according to established principles and best evidence, in partnership with the patient, their carers, and other health professionals as appropriate. Respond to patients' concerns and preferences, obtain informed consent, and respect the rights of patients to reach decisions with their doctor about their treatment and care and to refuse or limit treatment.
Prescribe drugs safely, effectively and economically	(a) Establish an accurate drug history, covering both prescribed and other medication
	(e) Provide patients with appropriate information about their medicines
The New Doctor- **Good clinical care**	
F1 doctors must:	
(c) demonstrate that they are taking increasing responsibility, under supervision and with appropriate discussion with colleagues, for patient care, putting the patient at the centre of their practice by:	(viii) helping patients to make decisions on their immediate and longer-term care (including self-care) taking into account the way the patient wants to make decisions (through shared decision-making, or by the doctor explaining the options and the patient asking the doctor to decide, or by the doctor explaining the options and the patient deciding)
	(ix) using medicines safely and effectively (under supervision) including giving a clear explanation to patients
Future Pharmacist- **Standard 10.2: The skills required in practice**	
Implementing health policy	Provide evidence –based medicines

	information
Validates therapeutic approaches, and supplies prescribed and over the counter medicines	Instruct patients in the safe and effective use of their medicines and devices
	Communicate with patients about their prescribed treatment
	Optimise treatment for individual patient needs in collaboration with the prescriber
Standards for pre-registration nursing education- **Domain 3: Nursing practice and decision-making**	
Adult nurses	must safely use invasive and non-invasive procedures, medical devices, and current technological and pharmacological interventions, where relevant, in medical and surgical nursing practice, providing information and taking account of individual needs and preferences
Mental health nurses	must help people experiencing mental health problems to make informed choices about pharmacological and physical treatments, by providing education and information on the benefits and unwanted effects, choices and alternatives. They must help people to identify actions that promote health and help to balance benefits and unwanted effects
Standards for pre-registration nursing education- **Essential skills cluster: Organisational aspects of care**	
9. People can trust the newly registered graduate to treat them as partners and work with them to make a holistic and systematic assessment of their needs; to develop a personalised plan that is based on mutual understanding and respect for their individual situation, promoting health and well-being, minimising risk of harm and promoting their safety at all times (All LO's at 'entry to the register' level)	16. Promotes health and well-being, self-care and independence by teaching and empowering people and carers to make choices in coping with the effects of treatment and the on-going nature and likely consequences of a condition including death and dying
	17. Uses a range of techniques to discuss treatment options with people
	18. Discusses sensitive issues in relation to public health and provides appropriate advice and guidance to individuals, communities and populations for example, contraception, substance misuse, smoking, obesity
Standards for pre-registration nursing education- **Essential skills cluster: Medicines management**	
35. People can trust the newly registered graduate to work as part of a team to offer holistic care and a range of treatment options of which medicines may form a part	3. Works confidently as part of the team and, where relevant, as leader of the team to develop treatment options and choices with the person receiving care and their carers
	4. Questions, critically appraises, takes

(All LO's at 'entry to the register' level)	into account ethical considerations and the preferences of the person receiving care and uses evidence to support an argument in determining when medicines may or may not be an appropriate choice of treatment
	Indicative content: The principles of holistic care, health promotion, lifestyle advice, over-the-counter medicines, self-administration of medicines and other therapies Observation and assessment Effect of medicines and other treatment options, including distraction, positioning, alternative and complementary therapies Ethical and legal frameworks
40. People can trust the newly registered graduate to work in partnership with people receiving treatments and their carers	1. Under supervision involves people and carers in administration and self-administration of medicines (LO: 'second progression point' level)
	2. Works with people and carers to provide clear and accurate information (LO: 'entry to the register' level)
	3. Gives clear instruction and explanation and checks that the person understands the use of medicines and treatment options (LO: 'entry to the register' level)
	4. Assesses the person's ability to safely self-administer their medicines (LO: 'entry to the register' level)
	5. Assists people to make safe and informed choices about their medicines (LO: 'entry to the register' level)
	Indicative content: Cultural, religious, linguistic and ethical beliefs, issues and sensitivities around medication Ethical issues relating to compliance and administration of medicine without consent Self-administration, assessment, explanation and monitoring Concordance Meeting needs of specific groups including self-administration, for example, people with mental health needs, learning disabilities, children and young people, adolescents and older adults

Appendix 8.2 Curriculum development consultation comments table

Stakeholder	Comments		Reply to comments
The European Patients' Forum	Competency areas	We agree with the competency areas outlined, including their titles. We particularly welcome the reference to building a partnership and shared decision-making, which are in our view key components to improve adherence.	Thank you for your comment.
	Competencies	We generally support the competencies outlined: we welcome the idea to have "listening" and "communicating" as overarching competences, and we also agree with the competencies in area 3 as they outline the key steps of a consultation in a shared or collaborative decision-making model. For Competency 4 the overarching statement could be expanded to "has up to date knowledge of area of practice of wider health and social services". Integration of care between health and social services is fundamental to improve the quality of care for the patients, and could also be a factor in improving adherence. One competency that could be modified is "deciding": We would suggest "informing and deciding", as the process of informing the decision is a crucial part of the consultation, and this is well reflected in the content of this competence, but could be better highlighted in the title. Regarding competency "monitoring" it would be good to add some reference taking account of the new EU pharmacovigilance legislation, which when implemented will give options for patients everywhere to report adverse reactions directly to competent authorities in addition to health professionals. While in EPF's view the patient-health professional relationship should remain central, patients often cite a perceived lack of interest, or lack of listening, by health professionals as the reasons for wanting to report directly. It is therefore important that a relationship of trust is established and patients are encouraged to turn to their health professional in the first instance	Thank you for your comments. We agree, this change has been made. We appreciate the point, but the process of informing the decision is already addressed in 'Communicating'. We appreciate the point and have amended the wording of attribute 1 in this competency area accordingly.

		concerning any suspected adverse reactions.	
	Listening	We agree with the attributes. Treating the patient as an equal partner, with valid and cogent health beliefs and expert knowledge of their own, is essential for shared decision-making. We welcome the recognition here of the changing role of the patient, from a passive recipient to an active participant in their own healthcare. We welcome particularly the idea to reassure the patient on timing, as time constraints for certain categories of healthcare professionals poses a significant practical problem and can undermine the building of a partnership for adherence. Furthermore, patients are often not aware of the possibility to request a longer than normal consultation even where such a possibility exists. We would also suggest possibly adding to the glossary the definitions for the terms "shared decision-making" and "concordance" (see final comments).	Thank you for your comments. We have now added a reading list that includes definitions for these terms.
	Communicating	The attributes outlined are a good basis towards establishing a shared understanding during the consultation. Improving the communication and interaction skills of healthcare professional is a key demand of patients. In our view, an essential counterpart to the informed and empowered patient is a health professional who welcomes this, and creates through their own behaviour an enabling environment for partnership and dialogue. Regarding the use of aids, we would like to highlight that many tools to enhance communication with the patients are available, including from patient organisations, such as decision aids, coaching and question prompts which could be more widely shared and used. Possibly you are already aware of many such tools, but EPF would be happy to provide further information regarding this. Attribute 2 could be modified to: Shares knowledge and information in a way and a	Thank you for your comments. We agree and examples have been included. We appreciate the point but

		language the patient understands, throughout the consultation. It is important that healthcare professionals avoid using medical jargon and explain medical terms as far as possible, and maintain an appropriate communication at all time during the consultation; possibly this point could be further clarified.	have amended the text in 'Monitoring' rather than in 'Communicating' as this applies to all consultations.
	Context	EPF agrees with the attributes outlined. We think it is particularly important that patients' preferences as to their degree of involvement in the decision are taken into account. There are clearly differences between patients, but many patients particularly with chronic conditions, would welcome the opportunity to get more involved given the opportunity and environment to do so.	Thank you for your comment.
	Knowledge	EPF agrees with the attributes outlined as they address two key issues: updating the professional's knowledge on the one hand, and communication with other healthcare professionals in the team around the patient as necessary on the other hand. The attribute "shares up-to-date information on specialist support and community resources" is particularly pertinent: patients need and want information on many topics besides treatment, therapies and disease management: prevention, lifestyle, social and peer support, patient education and reimbursement options. Healthcare professionals, if they cannot provide such information themselves, should be able to point patients to other sources or contacts where they can ask for such information. These sources include relevant patient organisations. Attribute 2 could be modified to "maintains an up to date knowledge appropriate to own role, including medical and technical knowledge, and soft skills." While updating medical and technical knowledge is essential, healthcare professionals should also develop and update "soft skills" such as communication with patients and carers. Attribute 4 could be modified to "refers to other healthcare professionals and social services as required or requested". As we mentioned in the question above, healthcare professionals should be able to point out relevant sources or contact for	Thank you for your comments. We appreciate the point and have included professional skills. We agree, this change has been made.

		social support**.** A specific reference could also be made to communicating with the patient's care coordinator when necessary/requested.	
	Understanding	We agree with the attributes as outlined. Point 4 is crucial for a genuine partnership. Point 1 is also fundamental, as many circumstances have to be taken into account. A more comprehensive list of examples could be developed and appended for more clarity on factors healthcare professionals may need to consider during the consultation, such as age, gender, psychological issues, mental health, social isolation, lifestyle issues, low health literacy, socio-economic/financial factors. All of these can have an influence on health and on adherence to treatment.	Thank you for your comments. We appreciate the point and have amended the wording in this competency area accordingly.
	Exploring	We welcome the attributes outlined. They take into account the perspective of the patient and provide a basis for a meaningful dialogue between the healthcare professional and the patient. Point 4 is very important as people's personal beliefs concerning medicines have been shown to be an important factor in adherence.	Thank you for your comments.
	Deciding	We agree with all points and they are all fundamentally important. Regarding point 2 we would reiterate that clear, accurate and understandable information is key to improving patients' adherence to the agreed treatment plan, but the important thing is to have a genuine, two-way-exchange. Patients provide information that contribute to the shared decision-making process. It is a key role of the health professional to empower patients to convey their health beliefs, provide their perspective and participate actively in the consultation. This point therefore links very closely to the "Communication" area. Attribute 2 could be further developed: "provide full, accurate and understandable information about the pros and cons of all treatment options including side effects and benefits, possible implications of long term use, and possible impacts on the patient's daily life.**"**	Thank you for your comments. We appreciate the point, have included the word understandable and the phrase "benefits, effects and

		The patient's understanding of the information should be checked. It is particularly important to convey information about the benefits of the treatment as well as risks, and reasons why the patient should not discontinue treatment without talking to their health professional. We would suggest amending attribute 6 to: "Discuss the patients preferred option for treatment": this formulation would make it clearer that patients' preference should also be taken into account at this stage, and that ultimately if the beliefs of both patients and healthcare professionals carry equal value, the most important choices are those made by the patients. We would propose adding a last point: "Provides a clear written recap of the agreed plan or treatment, tailored to the needs of the individual patient." Providing written information can be essential for patients especially where time constraints prevent an extended discussion. Patients should furthermore always be encouraged to come back with questions arising after the consultation.	risks (e.g. side effects)…". We appreciate the point and have clarified this point in 'Exploring'. We agree, this change has been made. We appreciate the point, but feel that this is already embodied in the wording of attribute 7. We agree, this has been added to 'Monitoring'.
	Monitoring	This area includes the main attributes to ensure that patients have information regarding follow-up, when they should consider stopping their treatment or not, and when to consult a health professional again. Attribute 1 could be modified as follow: "Ensures that the patient knows what to do if their symptoms change, do not improve, or if a problem arises." Many patients are not aware that medicines do not work in every patient. They may feel more reluctant to tell their healthcare professional that the treatment is not having any effect at all, than to discuss adverse effects.	Thank you for your comments. We agree, this change has been made.

		An attribute which could be added is to monitor that patients' needs for information are met following the consultation. This would help in closing the gap between patients' need for more information and healthcare professionals' overestimation of the amount of information they provide[1]. [1] This gap is highlighted in several studies including: Coulter, A. et al (1998) Informing patients: an assessment of the quality of patient information materials. London: King's Fund; Coulter, A. et al (1999) 'Sharing decisions with patients: is the information good enough?'. British Medical Journal, 318: 318-322.	We appreciate the point, and feel that this is embodied in 'provides ongoing information, support and feedback', which has been added to 'Monitoring'.
	Next steps	We would recommend considering inclusion of the concept of concordance[2] in the glossary, as in our view concordant consultation processes are more likely to result in higher adherence by patients and establish a therapeutic alliance. The definition of patient should be more inclusive: patients comprise human beings in need of or receiving health care services; and treatment can include not only medicines, but also medical devices and other forms of therapy. We welcome the explicit reference to family and carers' possible involvement in shared decision-making and we think this should be maintained, as they need adequate information and support from healthcare professionals to carry out their role. Dialogue between healthcare professionals and carers is also crucial, to take into account their needs and viewpoints. We feel that the title of the framework is somewhat negative. "Prevention and management of patient non-adherence to medications" implies that the non-adherent patient is a problem that needs to be managed. We propose that this should be worded in a more positive way, e.g. "management and support of patient adherence to therapies" (which incidentally also includes non-pharmacological therapies).	Thank you for your comments. We have now added a reading list that includes a definition of concordance. We appreciate the point, but this framework is focused on adherence to medicines. We agree, the title has been changed to managing and supporting medicines adherence.

		As regards the dissemination and uptake of this competency framework, we would like to highlight that patient organisations can educate and train patients to be informed and empowered to participate in shared decision-making. They can also contribute to the design and delivery of communications training for health professionals. Many patient organisations have developed special tools for information and training of healthcare professionals, either on a specific condition or to develop a holistic approach to patient care. These can, for example, take the form of workshop formats with patient-doctor interaction, special presentations, films, and materials as well as structured patient dossiers for communicating with professionals. EPF and our members are happy to share experiences in this area. EPF would also be happy to support the effective dissemination of this competency framework to our European-wide membership (currently 51 member organisations, see our website. We see this framework as an important step in the recognition of the importance of patient involvement. Building partnership between patients' and healthcare professionals' organisations is necessary to share perspectives and understandings of the competencies and attributes outlined in this framework, and to develop initiatives to realise the principles outlined here in clinical practice. EPF works closely at EU level with organisations representing health professionals, such as pharmacists (PGEU), doctors (CPME), medical specialists (UEMS) and nurses (EFN). Some examples of how patients' and healthcare professionals' organisations can work together to put in place adherence interventions that work were presented at a recent event held at the European Parliament by EPF, CPME, PGEU and EFPIA (the pharmaceutical industry association) – please see EPF's website for more information.	

		[2] EPF uses the terms as defined in Horne, R: "Compliance, adherence and concordance: implications for asthma treatment", *Chest*, 2006;130;65-72; and *Concordance, adherence and compliance in medicine taking. Report for the National Co-ordinating Centre for NHS Service Delivery and Organisation R&D*, December 2005.	
UK General Medical Council	Thank you for the opportunity to comment on the consultation document which describes the background to the development of the curriculum above. The key features of the proposed competency framework are very much akin to the generic expectations for undergraduate students in medical schools, particularly around communication, knowledge and working with patients. In the context of non-adherence to medications, these are particularly important themes. The standards and outcomes which cover these and many other areas, are contained in our document *Tomorrow Doctors.* This was last revised in 2009 and can be accessed through the following link: http://www.gmc-uk.org/education/undergraduate/tomorrows_doctors.asp. The section, *Outcomes 2, The doctor as a practitioner*, paragraph 17(e), *Prescribe drugs safely, effectively and economically,* requires students to understand the principles of giving patients appropriate information about their medicines.		Thank you for your comments.
Professor Karin Kjellgren, Professor of Nursing Science, University of Gothenburg and Linköping University,	Competency areas	They are well defined. Could sharing a decision be sharing a goal? Perhaps it would be of importance to have an area with the aim to improve or develop strategies for prevention and management	Thank you for your comment. We appreciate the point. The competency areas have been renamed and improving adherence strategies has been added to the curriculum.
	Competencies	In some way the competencies have an approach of paternalism by the words exploring, deciding. The words mastery and autonomy would be more appropriate from the patients point of view	Thank you for your comment. We have amended the wording of attributes to avoid

Sweden		To include: Sharing?	creating any impression of paternalism. 'Exploring' is used because this is a framework for health professionals, but in 'Deciding' we have emphasised that the patient's decision should be accepted.
	Listening	They are written from the perspective of providers. Is it possible to be more mutual?	Thank you for your comment. This is because it is a framework for health professionals rather than patients, but see the point about paternalism above.
	Communicating	They are written from the perspective of providers. Is it possible to be more mutual?	Thank you for your comment. This is because it is a framework for health professionals rather than patients, but see the point about paternalism above.
	Context	They are written from the perspective of providers. Is it possible to be more mutual?	Thank you for your comment. This is because it is a framework for health professionals rather than patients, but see the point about paternalism above.
	Knowledge	Perhaps it would be better to use the word understanding instead of knowledge in some sentences	Thank you for your comment. The word knowledge is only used once and in specific

			relation to maintaining a knowledge base.
	Understanding	This attributes are appropriate	Thank you for your comment.
	Exploring	Could exploring be changed to sharing?	Thank you for your comment. 'Exploring' is used because this is a framework for health professionals
	Deciding	Could deciding be changed to set goals	Thank you for your comment. We appreciate the point, but feel that 'deciding' is a broader term.
	Monitoring	Monitoring to be able to master the health problem?	Thank you for your comment. We appreciate the point, but this is a framework for health professionals rather than patients.
	Next steps	A more condensed curriculum and less of checkpoints would lead to a better understanding and easier to get an overview of the scope of the competency framework.	Thank you for your comment. An overview of the scope of the competency framework is provided in figure 1.
Dr Ilse Hellermann-Geschwinder, Medical University of Graz, Austria	Competency areas	1 to 5 are basics; but: 6,7 and 8, do you really want to discuss that with all the professionals concerned (nurse, pharmacist AND physican?) Delete 6,7,8 - The more actors are involved, the less adherence you can expect	Thank you for your comment. This could be minimised by effective sharing of information between professionals
	Competencies	These are basics	Thank you for your comment.
	Listening	ok	Thank you for your comment.
	Communicating	ok	Thank you for your comment.
	Context	ok	Thank you for your comment.

	Knowledge	1 is unlikely to be achieved, 2 to 7 are fine. Include legal aspects	Thank you for your comment. We appreciate the point, and have amended the text to take account of professional issues such as legal aspects
	Understanding	[no comments]	
	Exploring	[no comments]	
	Deciding	[no comments]	
	Monitoring	[no comments]	
	Next steps	[no comments]	
Dr. Siún O' Flynn, Head of Medical Education, School of Medicine University College Cork, Ireland	Competency areas	Broadly agree. Perhaps not an issue in the UK but cost is an issue elsewhere in compliance – perhaps this should feature in the exploration phase, Personally I also feel the risks of partial compliance have to be detailed in certain situations eg HIV ,TB ,Hep B where the risk extends beyond the individual and here there is justifiable unilateral decision making at times perhaps also duration of therapy should factor –ensure a patients/ medics/other relevant parties understand why, when, how much does it cost , how long, what happens if I don't take it at all , what happens if I sometimes take it /where can I find out more, what will be followed up– before a decision is reached the punchier the better. As presented I feel many of my colleagues – other overburdened hospital doctors would dispose of this document laudable as it is but are more likely to respond to something snappy and accessible presented along the lines of above. Delete any? No but I find that there is a somewhat artificial divide between 5 and 6	Thank you for your comments. We appreciate the point. The wording of the points in 'Exploring' and 'Supporting' (formerly 'Monitoring') have been amended to take factors such as cost into account. Although an overview of the competency framework is provided (figure 1), we intend to produce a separate short summary to facilitate this.
	Competencies	Broad and inclusive but possibly aspirational as opposed to practical. The simpler and snappier a framework is the more likely it is to be adopted and translated into practice – I suspect 8 steps with the need to read supporting documentation to identify what each step entails will secure participation ion those	Thank you for your comment.

		already interested in the area only	
	Listening	Broadly agree	Thank you for your comment.
	Communicating	Broadly agree	Thank you for your comment.
	Context	Broadly agree	Thank you for your comment.
	Knowledge	Broadly agree	Thank you for your comment.
	Understanding	Cost is a significant factor in Ireland and elsewhere	Thank you for your comment. We appreciate the point, and have added other examples of factors.
	Exploring	I feel that outcomes of partial compliance need to be explored, and what can happen in the first few days or what you may notice…	Thank you for your comment. We appreciate the difference, and have added a point about this in section 2.4 (how to use this framework). We agree, and feel that this is now embodied in the word "effects" in the new phrase "benefits, effects, risks and uncertainty".
	Deciding	Broadly agree	Thank you for your comment.
	Monitoring	Discusses what review entails – e.g. follow up bloods etc	Thank you for your comment. We agree, this has been added to attribute 2.
	Next steps	Make the framework very accessible to practice – some of the overarching headings require reading of the supporting text before they can really be understood– a sure way to ensure only the converted will read it. I would be very influenced by patient input also.	Thank you for your comment. The supporting text in the same box as the heading to facilitate ease of use.
Jeffrey Atkinson	Competency areas	I had some difficulty with the geographical scope "Europe-wide". Does the latter refer to the EU member states? If so, how does it fit in with the directive	Thank you for your comments.

Executive Director of the PHARMINE project. Emeritus professor of pharmacology University of Nancy, France		2005/36/EC? Or does it refer to the EHEA? If so, how does it fit in with the Bologna declaration? How does it fit in with national frameworks in the EU e.g. that of the French Chamber of Pharmacists (http://www.ordre.pharmacien.fr/fr/bleu/index4.htm)	These issues are dealt with in a new section 'Links to other frameworks and curricula' (section 1.3).
		Does it exclude other professions such as dentists and midwives that are also involved in patient compliance?	It is principally aimed at doctors, nurses and pharmacists but is also of relevance to other health professionals (this point has been clarified in section 2.3).
		The 8 competencies are split up into 3 competency areas, and yet they are numbered 1 through 8. The latter suggests some sort of chronology in application ("listening" to "monitoring") that is somewhat in conflict with the chronology of the competency areas ("building a partnership" to "sharing a decision"). I would prefer the "1 through 8" chronology.	We appreciate the point and have renamed the competency areas.
		I had a problem with the glossary and the definition of competency. The word has its origins in the French word "*compétent*" meaning "ability to perform" and the Latin "*competo*-" that introduces the notions of adequacy and attribute. The words "quality", "characteristic" and "performance" do not completely translate these aspects. This is important for those whose mother tongue is not English. In PHARMINE and at EAFP meetings we have had lively discussions with our UK partners as to what "competence/y" really means and to date the issue is not crystal clear. If we are to inculcate our pharmacy students with such notions then we had better be certain that we understand them.	This has been addressed in amended text in sections 1.2 and 1.3.
		Furthermore it is stated that "Competencies can be described as a combination of	We appreciate the point and

		knowledge…" (page 6), then on page 7 knowledge is described as a competency *per se*. Again this may be confusing for those with a limited knowledge of English. Communicating is surely a competency that is important in all 3 areas not only "building a partnership"? You could maybe include some notion of the specific patient-medicine interaction. Non-adherence to digitalis medication in an elderly patient with dementia will not be the same problem as non-adherence to antihypertensive treatment with a beta-blocker in a 40+ year old executive.	can clarify that the use of the word 'knowledge' in this framework relates to specific knowledge on managing and supporting adherence. We appreciate the point. The competency areas have been renamed. We appreciate the difference, and have added a point about this in section 2.4 (how to use this framework).
	Competencies	[no comments]	
	Listening	I wonder whether points 1 and 2 - that are very similar - could they not be grouped together. Point 8 raises the idea of "diversity" – of what exactly? Where is the "knowledge and skills framework" that is referred to in the lower box?	Thank you for your comment. We agree, this change has been made More detail has been included Reference to this has been removed
	Communicating	Point 5: "aids": could you give some examples?	Thank you for your comment. Examples have been added.
	Context	[no comments]	
	Knowledge	[no comments]	
	Understanding	[no comments]	
	Exploring	[no comments]	
	Deciding	Point 6: "negotiates"? Where is this going? How much leverage does the patient have?	Thank you for your comment.

			A reworded point 1 clarifies that ultimately the patient's decision should be accepted.
	Monitoring	The paradigm for monitoring extends to contact details but no further. Is there not a need to establish how monitoring will be performed?	Thank you for your comment. This has been amended.
	Next steps	The FP7 theme health programme presumably is looking at concrete outcomes and namely how this project will actually improve the prevention and management of patient non-adherence to medicines. How do you propose to test this? What sort of evidence can you produce?	Thank you for your comments. This will be taken into consideration in the final report.

Appendix 8.3 National self assessment study interview schedule

For each of the policy recommendations that have been implemented, we will ask officials the following questions:

- Why did you decide to implement this action/development?
- Have any benefits been observed as a result of implementation?
- Have any negative consequences been observed as a result of implementation?
- What barriers have you encountered in implementing this item?
- How did you perceive the roles of the various stakeholder groups (for example the government, healthcare professionals, patient organisations, pharmaceutical industry) in implementation of the item?
- Have you found that implementation has been differentially effective in various healthcare settings, systems, and population segments?

For each of the policy recommendations that have not yet been implemented but feature in future planning, we will ask officials the following questions:

- Why have you decided to include this particular action in the future planning for medication adherence in your nation?
- What barriers are you likely to encounter in implementing this action?
- How do you perceive the roles of the various stakeholder groups (for example the government, healthcare professionals, patient organisations) in implementation?
- Do you think that implementation will be differentially effective in various healthcare settings, systems, and population segments?

For each of the policy recommendations that have not been implemented and do not feature in the future planning for the nation, officials will be asked the following questions:

- Why have you decided not to include this development for medication adherence in the future planning for your nation?
- If implementation of the recommendation is not feasible in your nation, are there ways in which this action could be modified or adapted, or are there any feasible alternatives?

All officials will also be asked the following questions:

- How do you perceive the various policy recommendations as fitting together? Are there any recommendations that you think would be best implemented in combination with other recommendations?
- What are your models of best practice with regard to medication adherence?
- What are your priorities for policy development in medication adherence and how do these priorities reflect of differ from the ABC policy recommendations?

Appendix 8.4 Examples of service provision for medication adherence in seven European countries

Country	Service provision examples
Estonia	• Patient education campaign, entitled “Ask about medicines”, was initiated in pharmacies.
Finland	• Use of treatment guidelines. • Dose-unit services available at pharmacies, with reimbursement for patients aged over 75 years or taking six or more medicines. • Medication review available for those patients receiving reimbursed dose-dispensing services. • Home service available, in which nurses care for patients within the patients’ homes. • Specialist nurses for patients with long-term diseases, for example diabetes and asthma, work in most healthcare centres. • Discussion on medicines-taking behaviour offered by pharmacists.
Germany	• Patient information leaflets provided within medication packaging. • Information on medicinal products available from doctors and pharmacists. • Patient leaflet produced by the Federal Ministry of Health, containing eight tips on how to behave in relation to medicinal products. Approximately five million copies were produced and distributed to all public pharmacies, patient organisations and some hospitals, and included within newspapers for doctors and pharmacists.
Ireland	• Medication reviews available, although these are not carried out routinely and largely take place in teaching hospitals with clinical pharmacists on a patient’s admission and discharge. • Discussion of medicines issues offered by community pharmacists

	(required under professional code of practice). • Patient consultation areas provided within community pharmacies. • “Ask your pharmacist” campaigns, run by the Pharmaceutical Union. • Targeted information campaigns, carried out by the health authority’s Health Promotion Unit. • Patients’ views gathered through surveys and consultations with patient organisations. • Community interventions teams available for patients most at risk. These teams sometimes provide home pharmacy and weekly monitored dose dispensing services. • The Patient’s Charter 1994 outlines the rights of the hospital patient. • Medicines information is provided on official websites, such as those of the Health Service Executive, Regulatory Authorities, Irish Medicines Board, and the Health Information and Quality Authority. • The Health Service Executive provides helplines. • Collaborations with the Royal College of Physicians, for instance on public lectures. • Chronic disease home monitoring devices are available.
Lithuania	• Full information about medicinal products registered in Lithuania can be accessed through the State Drug Control Agency. Information is provided in Lithuanian and sometimes in other languages. • Advice on treatment options and medicines-taking is provided by pharmacists.
Malta	• An approved patient information leaflet is provided within every medicine packet. The leaflets are written in English for most products. • Patient information leaflets can be downloaded from the Medicines Authority website. • Radio and television programmes broadcast to highlight the

	availability of patient information and information to support patients' choices, run by the Medicines Authority. • Public awareness campaign entitled "Know Your Medicines", run by the Medicines Authority. • Patient information leaflets provided on buying medicines over the internet, falsified products, and generics and originator medicines, to empower the patient to make decisions about their medication and support national medicines use. • Patients are able to discuss medicines-related concerns with pharmacists. This service is free of charge and available everywhere. • Leaflets of the "Know Your Medicines" campaign emphasise the roles of pharmacists and doctors in offering support to patients. • Discussion on treatments offered by doctors. • "Pharmacist of your choice" initiative, provided by the National Health Service, has been rolled out across approximately half of Malta. Pharmacists evaluate prescribed medicines and feedback is given to the patient, akin to a medication review. • Multidisciplinary teams are active in some clinical areas, such as rheumatoid arthritis, and offer patients consultations with a clinical pharmacist. These patients also tend to be seen regularly and are monitored closely in terms of the effects of their medication.
Netherlands	• Medicines information leaflets are available from general practitioners.