Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence

Full Guideline

January 2009

National Collaborating Centre for Primary Care

Citation

Nunes V, Neilson J, O'Flynn N, Calvert N, Kuntze S, Smithson H, Benson J, Blair J, Bowser A, Clyne W, Crome P, Haddad P, Hemingway S, Horne R, Johnson S, Kelly S, Packham B, Patel M, Steel J (2009). Clinical Guidelines and Evidence Review for Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners.

ROYAL COLLEGE OF GENERAL PRACTITIONERS

14 Princes Gate, Hyde Park, London, SW7 1PU

www.rcgp.org.uk

Registered charity No 223106

Table of Contents

Preface

The prescription of medicines is a core element of the delivery of modern health care. Medicines are widely used not only to relieve symptoms and cure conditions but to prevent ill health in the future. Medical advances, combined with an ageing population, have resulted in many patients taking multiple medicines in complex regimes. There is an increasing number and diversity of healthcare professionals involving in prescribing, dispensing or reviewing medicines. Prescribing was once the preserve of the medical profession but prescribing rights are now available to other health professionals either as independent or supplementary prescribers.

Medicine-taking is a complex human behaviour and patients evaluate medicines, and the risks and benefits of medicines using the resources available to them. Unwanted and unused medicines reflect inadequate communication between professionals and patients - about health problems and how they might be treated, and about patients' ongoing assessment and experience of treatments. This guideline will be of help to all healthcare professionals by providing guidance on how to involve patients in the decision to prescribe medicines and on how to support patients in their subsequent use of medicines. The recommendations include advice to healthcare professionals to ensure there are robust mechanisms to ensure communication between the many professionals who may be involved in each patient's care.

The guideline has been developed using standard NICE methodology. Patient involvement and adherence are central to medicine –taking yet these areas are less well researched than medicines themselves. The guideline development process has highlighted the areas in which evidence is lacking and the Guideline Development Group has indicated those areas they consider high priority for research at the end of the guideline. Developing recommendations from the evidence might have been difficult if not for the commitment and expertise of the Guideline Development Group. I am

extremely grateful to them for the good humour and skill they brought to their task.

Norma O' Flynn
Clinical Director,
National Collaborating Centre for Primary Care

Introduction

The prescription of medicines is central to medical care and drug costs amount to around 10% of NHS expenditure. In 2006-2007, the NHS in England spent £10.6billion on drugs, around three quarters of which was in primary care. It is thought that between a half and third of all medicines prescribed for long term conditions are not taken as recommended [1]. The estimated drug cost of unused or unwanted medicines in the NHS is around £100million annually [2].

A Cochrane review "Interventions for enhancing medication adherence" [3] concluded that improving medicines taking may have a far greater impact on clinical outcomes than an improvement in treatments.

If the prescription was appropriate then this may represent a loss not just for patients but also for the healthcare system and society. The costs are both personal and economic. Non adherence may limit the benefits of medicines resulting in lack of improvement or deterioration in health. The economic costs are not limited to wasted medicines but also include the knock-costs arising from increased demands for healthcare if health deteriorates.

Adherence is defined as 'the extent to which the patient's behaviour matches agreed recommendations from the prescriber'. Adherence shifts the balance between professional and patient to suggest there should be agreement between professional and patient about the prescriber's recommendation.

Nonadherence is a large problem but it should not be seen as the patient's problem. Rather, it represents a limitation in the delivery of healthcare, often due to a failure to fully agree the prescription in the first place or to identify and provide the support that patients need later on.

Addressing nonadherence is not about getting patients to take more medicines per se. It starts with an understanding of patients' perspectives of medicines and the reasons why they may not want or are unable to use them [4] [5]. Practitioners have a duty to help patients make informed decisions about treatment and use appropriately prescribed medicines to best effect.

There are many causes of nonadherence but they fall into two overlapping categories: intentional and unintentional. Unintentional nonadherence occurs when the patient wants to follow the agreed treatment but is prevented from doing so by barriers that are beyond their control. Examples include poor recall or comprehension of instructions, difficulties in administering the treatment, inability to pay for the treatment or simply forgetting to take it. Unintentional nonadherence is related to limitations in the persons' capacity and resources affecting their ability to implement their intention to adhere. Intentional nonadherence occurs when the person decides not to follow the treatment recommendations.

This guideline provides recommendations on the process of involving patients in decisions about medicines and on supporting the patient in their adherence to medicine. We have not made separate recommendations for carers and families. The principal relationship is between patient and healthcare professional and the patient has a right to decide who should be involved in their care. With patient consent, carers should have access to appropriate levels of information and support.

There are an increasing number of healthcare professionals now involved in prescribing of medicines, dispensing and reviewing of medicines. It is not within the remit of a guideline to recommend which healthcare professional carries out these roles. Healthcare professionals need to be aware of and work within legal and professional codes.

Patient-Centered Care

This guideline offers best practice advice on how to involve patients in decisions about prescribed medicines and how to support adherence.

All NICE clinical guidelines state that treatment and care should take into account patients' needs and preferences and patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to each patient's needs.

If the patient agrees, families and carers should also have the opportunity to be involved in decisions about treatment and care. Families and carers should be given the information and support they need.

If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health guidelines – 'Reference guide to consent for examination or treatment' (2001) (available from www.dh.gov.uk). Healthcare professionals should also follow the code of practice that accompanies the Mental Capacity Act (summary available from www.publicguardian.gov.uk).

Key principles

- Healthcare professionals should adapt their consultation style to the needs of individual patients so that all patients have the opportunity to be involved in decisions about their medicines at the level they wish.

- Establish the most effective way of communicating with each patient and, if necessary, consider ways of making information accessible and understandable (for example, using pictures, symbols, large print, different languages, an interpreter or a patient advocate).

- Offer all patients the opportunity to be involved in making decisions about prescribed medicines. Establish what level of involvement in decision-making the patient would like.

- Be aware that increasing patient involvement may mean that the patient decides not to take or to stop taking a medicine. If in the healthcare professional's view this could have an adverse effect, then the information provided to the patient on risks and benefits and the patient's decision should be recorded.

- Accept that the patient has the right to decide not to take a medicine, even if you do not agree with the decision, as long as the patient has the capacity to make an informed decision and has been provided with the information needed to make such a decision.

- Be aware that patients' concerns about medicines, and whether they believe they need them, affect how and whether they take their prescribed medicines.

- Offer patients information that is relevant to their condition, possible treatments and personal circumstances, and that is easy to understand and free from jargon.

- Recognise that non-adherence is common and that most patients are non-adherent sometimes. Routinely assess adherence in a non-judgemental way whenever you prescribe, dispense and review medicines.

- Be aware that although adherence can be improved, no specific intervention can be recommended for all patients. Tailor any intervention to increase adherence to the specific difficulties with adherence the patient is experiencing.

- Review patient knowledge, understanding and concerns about medicines, and a patient's view of their need for medicine at intervals agreed with the patient, because these may change over time. Offer repeat information and review to patients, especially when treating long-term conditions with multiple medicines.

1   Guidance

The following guidance is based on the best available evidence. These recommendations apply to all healthcare professionals who prescribe or dispense medicines or who have a role in making decisions about medicines with patients. Healthcare professionals are reminded of their duty under the Disability Discrimination Act (2005) to make reasonable adjustments to ensure that all people have the same opportunity for health.

1.1   Recommendations

Patient involvement in decisions about medicines
Communication

Good communication between healthcare professionals and patients is needed for involvement of patients in decisions about medicines and for supporting adherence. Some patients may find it easier to communicate with their healthcare professional than others.

1.1.1   Healthcare professionals should adapt their consultation style to the needs of individual patients so that all patients have the opportunity to be involved in decisions about their medicines at the level they wish.

1.1.2   Consider any factors such as physical or learning disabilities, sight or hearing problems and difficulties with reading or speaking English, which may affect the patient's involvement in the consultation.

1.1.3   Establish the most effective way of communicating with each patient and, if necessary, consider ways of making information accessible and understandable (for example, using pictures, symbols, large print, different languages, an interpreter or a patient advocate).

1.1.4   Encourage patients to ask about their condition and treatment.

1.1.5   Ask patients open ended questions because these are more likely to uncover patients' concerns.

1.1.6   Be aware that the consultation skills needed for increasing patient involvement can be improved.

Increasing patient involvement

Patient involvement in the decision making process requires that healthcare professionals acknowledge patients' views about their condition and its treatment, and that both healthcare professional and patient have a role in making decisions about treatment. Simple interventions to increase patient involvement do not necessarily increase the overall length of consultation and may be justified by benefits, particularly over the course of a long term condition.

1.1.7   Offer all patients the opportunity to be involved in making decisions about prescribed medicines. Establish what level of involvement in decision making the patient would like.

1.1.8   Discuss with the patient why they might benefit from the treatment. Clearly explain the disease or condition and how the medicine will influence this.

1.1.9   Explain the medical aims of the treatment to patients and openly discuss the pros and cons of proposed medicines. The discussion should be at the level preferred by the patient.

1.1.10 Clarify what the patient hopes the treatment will achieve.

1.1.11 Avoid making assumptions about patient preferences about treatment. Talk to the patient to find out their preferences, and note any non verbal cues that may indicate you need to explore the patient's perspective further.

1.1.12 Healthcare professionals have a duty to help patients to make decisions about their treatment based on an understanding of the likely benefits and risks rather than on misconceptions.

1.1.13 Accept that patients may have different views from healthcare professionals about the balance of risks, benefits and side effects of medicines.

1.1.14 Be aware that increasing patient involvement may mean that the patient decides not to take or to stop taking a medicine. If in the healthcare professional's view this could have an adverse effect, then the information provided to the patient on risks and benefits and the patient's decision should be recorded.

1.1.15 Accept that the patient has the right to decide not to take a medicine, even if you do not agree with the decision, as long as the patient has the capacity to make an informed decision and has been provided with the information needed to make such a decision.

1.1.16 Assess the patient's capacity to make each decision using the principles in the Mental Capacity Act (2005) (www.opsi.gov.uk/ACTS/acts2005/ukpga_20050009_en_1). To lack capacity patients must: (a) have an impairment of or disturbance or malfunction of brain and mind, and (b) demonstrate lack of capacity to:

• understand the information relevant to the decision

• retain information for long enough to use it in the decision

• use or weigh information as part of the process of making the decision

• communicate the decision (whether by talking, using sign language or any other means).

1.1.17 If the patient has specific concerns, record a summary of the discussion, because this may be helpful in future consultations.

1.1.18 Encourage and support patients, families and carers to keep an up to date list of all medicines the patient is taking. The list should include the names and dosages of prescription and non prescription medicines and herbal and nutritional supplements. If the patient has any allergic or adverse reactions to medicines, these should be noted.

Understanding the patient's knowledge, beliefs and concerns about medicines

There is evidence that patients make decisions about medicines based on their understanding of their condition and the possible treatments, their view of their own need for the medicine and their concerns about the medicine.

1.1.19 Be aware that patients' concerns about medicines, and whether they believe they need them, affect how and whether they take their prescribed medicines.

1.1.20 Ask patients what they know, believe and understand about medicines before prescribing new treatments and when reviewing medicines.

1.1.21 Ask if the patient has any specific concerns about their medicines, whenever you prescribe, dispense or review medicines. These may include concerns about becoming dependent on medicines and concerns about adverse effects. Address these concerns.

1.1.22 Be aware that patients may wish to minimise how much medicine they take.

1.1.23 Be aware that patients may wish to discuss:

- what will happen if they do not take the medicine suggested by their healthcare professional

- non pharmacological alternatives to medicines

- how to reduce and stop medicines they may have been taking for a long time, particularly those known to be associated with withdrawal symptoms

- how to fit taking the medicine into their daily routine

- how to make a choice between medicines if they believe they are taking too many medicines.

Providing information

Patients need information about their condition and possible treatments if

they are to be involved in making informed decisions about medicines. The

format and content of the information provided should meet the needs of

individual patients.

1.1.24 Offer patients information about medicines before the medicines are

prescribed.

1.1.25 Offer patients information that is relevant to their condition, possible

treatments and personal circumstances, and that is easy to understand and

free from jargon.

1.1.26 Check that patients have any information they wish about medicines

when the medicines are dispensed.

1.1.27 Discuss information on medicines with the patient rather than just

presenting it. The discussion should take into account what the patient

understands and believes about the condition and treatment.

1.1.28 Do not assume that the patient information leaflets (PILs) that patients

receive with their medicines will meet each patient's needs. Address concerns

that patients may have after reading the standard PILs.

1.1.29 Patients differ in the type and amount of information they need and

want. Therefore the provision of information should be individualised and is

likely to include, but not be limited to:

• what the medicine is

• how the medicine is likely to affect their condition (that is, its benefits)

• likely or significant adverse effects and what to do if they think they are
  experiencing them

• how to use the medicine

- what to do if they miss a dose

- whether further courses of the medicine will be needed after the first prescription

- how to get further supplies of medicines.

1.1.30 Be careful not to make assumptions about a patient's ability to understand the information provided. Check with the patient that they have understood the information. Information for patients should be clear and logical and, if possible, tailored to the needs of the individual patient.

1.1.31 Suggest where patients might find reliable information and support after the consultation: for example, by providing written information or directing them to other resources (for example, NHS Choices [www.nhs.uk]).

1.1.32 Provide inpatients with the same information as patients in other settings. Information should include:

- what the medicine is

- how the medicine is likely to affect their condition (that is, its benefits)

- likely or significant adverse effects and what to do if they think they are experiencing them

- how to use the medicine

- what to do if they miss a dose

- whether further courses of the medicine will be needed after the first prescription

- how to get further supply after discharge.

Supporting adherence

Assessing adherence

Patients do not always take their medicines exactly as prescribed, and healthcare professionals are often unaware of how patients take their medicines. The purpose of assessing adherence is not to monitor patients but rather to find out whether patients need more information and support.

1.2.1 Recognise that non adherence is common and that most patients are non adherent sometimes. Routinely assess adherence in a non judgemental way whenever you prescribe, dispense and review medicines.

1.2.2 Consider assessing non adherence by asking the patient if they have missed any doses of medicine recently. Make it easier for them to report non adherence by:

- asking the question in a way that does not apportion blame

- explaining why you are asking the question

- mentioning a specific time period such as 'in the past week'

- asking about medicine-taking behaviours such as reducing the dose, stopping and starting medicines.

1.2.3 Consider using records of prescription re ordering, pharmacy patient medication records and return of unused medicines to identify potential non adherence and patients needing additional support.

Interventions to increase adherence

Patients may need support to help them make the most effective use of their medicines. This support may take the form of further information and discussion, or involve practical changes to the type of medicine or the regimen. Any interventions to support adherence should be considered on a

case by case basis and should address the concerns and needs of individual patients.

1.2.4   If a patient is not taking their medicines, discuss with them whether this is because of beliefs and concerns or problems about the medicines (intentional non adherence) or because of practical problems (unintentional non adherence).

1.2.5   Be aware that although adherence can be improved, no specific intervention can be recommended for all patients. Tailor any intervention to increase adherence to the specific difficulties with adherence the patient is experiencing.

1.2.6   Find out what form of support the patient would prefer to increase their adherence to medicines. Together, you and your patient should consider options for support.

1.2.7   Address any beliefs and concerns that patients have that result in reduced adherence.

1.2.8   Because evidence supporting interventions to increase adherence is inconclusive, only use interventions to overcome practical problems associated with non adherence if a specific need is identified. Target the intervention to the need. Interventions might include:

•   suggesting that patients record their medicine taking

•   encouraging patients to monitor their condition

•   simplifying the dosing regimen

•   using alternative packaging for the medicine

•   using a multi compartment medicines system.

1.2.9   Side effects can be a problem for some patients. If this is the case you should:

•   discuss how the patient would like to deal with side effects

- discuss the benefits, side effects and long term effects with the patient to allow them to make an informed choice

- consider adjusting the dosage

- consider switching to another medicine with a different risk of side effects

- consider what other strategies might be used (for example, timing of medicines).

1.2.10 Ask patients if prescriptions charges are a problem for them. If they are, consider possible options to reduce costs.

Reviewing medicines

Patients may use medicines long term. The initial decision to prescribe medicines, the patient's experience of using the medicines and the patient's needs for adherence support should be reviewed regularly. The patient's own list of medicines may be a useful aid in a medicines review.

1.3.1   Review patient knowledge, understanding and concerns about medicines, and a patient's view of their need for medicine at intervals agreed with the patient, because these may change over time. Offer repeat information and review to patients, especially when treating long term conditions with multiple medicines.

1.3.2   Review at regular intervals the decision to prescribe medicines, according to patient choice and need.

1.3.3   Enquire about adherence when reviewing medicines. If non adherence is identified, clarify possible causes and agree any action with the patient. Any plan should include a date for a follow up review.

1.3.4   Be aware that patients sometimes evaluate prescribed medicines using their own criteria such as their understanding of their condition or the symptoms most troubling to them. They may, for example, stop and start the

medicine or alter the dose and check how this affects their symptoms. Ask the patient whether they have done this.

Communication between healthcare professionals

Patients may be under the care of healthcare professionals from different disciplines and specialties at the same time; responsibility for patients' care may be transferred between healthcare professionals, and medicines reviews may be carried out by healthcare professionals other than the prescriber. Therefore good communication between healthcare professionals is required to ensure that fragmentation of care does not occur.

1.4.1   Healthcare professionals involved in prescribing, dispensing or reviewing medicines should ensure that there are robust processes for communicating with other healthcare professionals involved in the patient's care.

1.4.2   On transfer between services (for example, between hospitals and care homes or on discharge from hospital), give all patients and subsequent healthcare or other providers a written report containing:

- the patient's diagnosis

- a list of all medicines the patient should be taking

- clear identification of any new medicines that were started

- clear identification of any medicines that were stopped, with reasons

- clear information on which medicines should be continued after transfer from that service and for how long

- any known adverse reactions and allergies the patient has experienced

- any potential difficulties with adherence and any actions taken (for example, provision of a multi compartment medicines system).

1.4.3   Healthcare professionals involved in reviewing medicines should inform the prescriber of the review and its outcome. This is particularly important if

the review involves discussion of difficulties with adherence and further review is necessary.

1.2 Aim of the guideline

Clinical guidelines are defined as 'systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances.'

This guideline gives recommendations to clinicians and others on how to involve adults and carers in decisions about prescribed medicine.

1.3 How the guideline is set out

Both the evidence statements and narratives of the research studies on which our recommendations are based are found within each topic section. The evidence statements precede the narrative for each topic. Also included in each chapter is a brief explanation of why the GDG made the specific recommendations. The evidence tables with details of the research studies that describe the studies reviewed are found in Appendix C.

1.4 Scope

The guideline was developed in accordance with a scope given by the National Institute for Health and Clinical Excellence (NICE, 'the Institute'). The scope set the remit of the guideline and specified those aspects of the identification and management of medicines adherence to be included and excluded. The scope was published in April 2007 and is reproduced here in Appendix A.

During development the guideline title was Medicines Concordance. Stakeholder comment during consultation indicated that retaining the term concordance in the title was potentially misleading and unhelpful to healthcare professionals. NICE Guidance Executive agreed to the title Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence as this more clearly explains the content of the guideline.

Whom the guideline is intended for

This guideline is of relevance to those who work in or use the National Health Service (NHS) in England and Wales:

Population

Groups that will be covered

a) Adults, including those with co morbidities, learning disabilities or language and/or cultural differences.

Groups that will not be covered

Children and young people. However, the guideline recommendations may be considered for a child or young person who is deemed competent to express a view on their prescription.

Healthcare setting

All consultations with healthcare professionals in any NHS setting that relate to the initiation or review of prescribed medicine.

Areas that will be covered

a) Shared decision-making about medicines and medicine-taking as reported by the patient or carer. The guideline will focus on the barriers (such as communication difficulties, cultural issues, low health literacy and physical limitations), facilitators (including structural or procedural factors), beliefs and health behaviours that influence decision-making and adherence.

b) Shared decision-making about medicines and medicine-taking as reported by the healthcare professional. The guideline will focus on the barriers (such as communication difficulties, cultural issues and time), facilitators (including structural or procedural factors), beliefs and health behaviours that influence decision-making and adherence.

c) The effectiveness and cost-effectiveness of interventions to facilitate the process of shared decision-making about medicines (looking at time of intervention – before, during, or after the consultation with the healthcare

professional; and mode of delivery). The target of the intervention may be the patient, the carer, the prescriber, any healthcare professional providing ongoing support or a combination of these.

d) The effectiveness and cost-effectiveness of interventions to promote adherence in medicine-taking (looking at time of intervention – before, during, or after the consultation with the healthcare professional; and mode of delivery). The target of the intervention may be the patient, the carer, the prescriber, the dispenser or any other healthcare professional providing ongoing support or a combination of these.

e) The evidence on single or multiple medicines as it relates to issues around decision-making and adherence.

f) The skills and competencies required by prescribers to involve patient in decisions regarding prescribed medicines.

Areas outside the remit of the guideline

The administration of medicines will not be covered. Administration is defined as giving a medicine by introduction into the body (for example, orally or by injection), or by external application (for example application of an impregnated dressing).

1.5 Guideline Limitations

Guideline limitations are as follows:

- NICE clinical guidelines usually do not cover issues of service delivery, organisation or provision (unless specified in the remit from the Department of Health).
- NICE is primarily concerned with health services and so recommendations are not provided for social services and the voluntary sector. However, the guideline may address important issues in how NHS clinicians interface with these sectors.

- Generally, the guideline does not cover rare, complex, complicated or unusual conditions.

- It is not possible in the development of a clinical guideline to complete extensive systematic literature reviews of all pharmacological toxicity. NICE expects the guidelines to be read alongside the summaries of product characteristics.

1.6 Responsibility and support for guideline development

1.6.1 The National Collaborating Centre for Primary Care (NCC-PC)

The NCC-PC is a partnership of primary care professional associations and was formed as a collaborating centre to develop guidelines under contract to NICE. It is entirely funded by NICE. The NCC-PC is contracted to develop four guidelines at any one time, although there is some overlap at start and finish. Unlike many of the other centres which focus on a particular clinical area, the NCC-PC has a broad range of topics relevant to primary care. However, it does not develop guidelines exclusively for primary care. Each guideline may, depending on the scope, provide guidance to other health sectors in addition to primary care.

The Royal College of General Practitioners (RCGP) acts as the host organisation. The Royal Pharmaceutical Society and the Community Practitioners and Health Visitors' Association are partner members with representation from other professional and lay bodies on the Board. The RCGP holds the contract with the Institute for the NCC-PC.

1.6.2 The development team

The development team had the responsibility for this guideline throughout its development. They were responsible for preparing information for the Guideline Development Group (GDG), for drafting the guideline and for responding to consultation comments. The development team working on this guideline consisted of the:

- **Guideline lead**

  who is a senior member of the NCC-PC team who has overall responsibility for the guideline

- **Information scientist**

  who searched the bibliographic databases for evidence to answer the questions posed by the GDG

- **Reviewer (Health Services Research Fellow**)

  with knowledge of the field, who appraised the literature and abstracted and distilled the relevant evidence for the GDG

- **Health economist**

  who reviewed the economic evidence and assisted the GDG in considering cost-effectiveness

- **Project manager**

  who was responsible for organising and planning the development, for meetings and minutes and for liaising with the Institute and external bodies

- **Chair**

  who was responsible for chairing and facilitating the working of the GDG meetings

The members of the development team attended the GDG meetings and participated in them. The development team also met regularly with the Chair of the GDG during the development of the guideline to review progress and plan work.

Other guidelines normally have a Clinical Advisor who is someone with an academic understanding of the research in the area and its practical implications to the service, who advises the development team on searches and the interpretation of the literature. Due to the conceptual nature of the guideline topic and the different academic stances on explaining such behaviour, the development team chose not to have a formal Clinical Advisor.

1.6.3   The Guideline Development Group (GDG)

A Chair was chosen for the group and his primary role was to facilitate and chair the GDG meetings.

The GDG consisted of a diverse multidisciplinary group with an interest and/or expertise in medicines adherence. The Chair, a general practitioner with special interest in epilepsy identified by the NCC-PC, oversaw the work of the group.

Nominations for group members were invited from various stakeholder organisations, selected to ensure appropriate combination of members including healthcare professionals and patient representatives.

Each GDG member was expected to act as an individual expert in their own right and not as a representative of their parent organisation, although they were encouraged to keep their nominating organisation informed of the process.

Nominees who were not selected for the GDG were invited to act as Expert Peer Reviewers and were sent drafts of the guideline by the Institute during the consultation periods and invited to submit comments using the same process as stakeholders.

In accordance with guidance from NICE, all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships, and support from the healthcare industry. Details of these can be seen in Appendix E.

The names of GDG members appear listed below.

Full GDG members

Dr Henry Smithson (Chair)
General Practitioner; Senior Clinical University Teacher, Academic Unit of Primary Medical Care, Sheffield

Dr Peter Haddad

Consultant Psychiatrist, Greater Manchester West Mental Health NHS Foundation Trust; Honorary Senior Lecturer in Psychiatry, University of Manchester

Dr Jonathan Steel

General Practitioner, Gloucestershire; Chairman, GP Network, Royal College of Physicians

Dr Sean Kelly

Consultant Physician and Gastroenterologist, York Hospital; Honorary Senior Lecturer, Hull York Medical School

Dr Wendy Clyne

Assistant Director, Medicines Partnership Programme, NPC Plus, Keele University

National Collaborating Centre for Primary Care

Dr Norma O'Flynn
Guideline Lead and Clinical Director

Ms Elizabeth Shaw
Guideline Lead (until February 2007) and Deputy Chief Executive (until February 2008)

Ms Vanessa Nunes
Senior Health Services Research Fellow/Project Manager

Ms Julie Neilson
Health Services Research Fellow

Ms Stefanie Kuntze
Health Economist (until October 2008)

Dr Neil Calvert
Senior Health Economist

1.6.4   Guideline Development Group meetings

The GDG met on 12 occasions (with one two day GDG meeting), at approximately 2 monthly intervals over a period of 11 months and 6 weekly intervals over a period of 6 months to review the evidence identified by the project team, to comment on its quality and completeness and to develop recommendations for clinical practice based on the available evidence. The final recommendations were agreed by the full GDG.

1.7   Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

The GDG noted the generally poor quality of research in the area of medicines adherence and the potential clinical and economic gains that would accrue from the development of cost-effective, equitable and patient-centred interventions to support adherence to appropriate prescriptions The GDG believe that there is an urgent need to provide specific adherence funding streams to support structured programmes of research particularly where the health gains from medicines adherence are likely to be high.

The central theme underpinning this guideline is that adherence to medicines taking is a variable behaviour that should be based on informed choice and shared decision making, principally between the patient and the practitioner. Medicines carry the potential for harm as well as benefit and there are questions about what constitutes good prescribing and good medicine-taking. The key research agenda therefore relates to behaviour change for practitioners and patients to support the best use of medicines.
The research recommendations from this guideline are for research programmes which are described below under the themes of A): Developing effective, equitable interventions to support adherence to appropriately prescribed medicines B) Informed choice and shared decision making, C)

Support processes: prescribing-related consultations and medicines usage review and D) Groups for special consideration- vulnerable groups.

A): Developing effective, equitable interventions to support adherence to appropriately prescribed medicines.

Research Questions

1.   What are the most clinically effective and cost-effective methods for identifying and addressing the perceptual barriers (such as beliefs and concerns about medicines) which influence motivation to start and continue with treatment and the practical barriers (such as limitations in personal capacity and resources), which limit an individuals' ability to implement intentions to adhere to medicines?

Why this is important

Systematic reviews of adherence interventions show that although adherence can be improved, the effects were generally modest and there is considerable room for improvement. Few previous interventions have been systematically developed, using appropriate theoretical models, nor have they have been modelled and piloted with assessment of process variables as well as outcomes. We now know why previous interventions have failed, but also how we can improve the content, development and testing of new approaches. The challenges for research in medicines adherence are similar to those for other health-related behaviours such as smoking cessation, exercise and diet: how to influence and change behaviour. Interventions should be developed using an appropriate theoretical framework with a phased approach to testing that includes assessment of process (i.e. the things that are targeted for change) as well as outcomes and a need for an individual approach, as recommended in the Medical Research Council Framework. There are particular questions relating to vulnerable groups (see Section C). Interventions may need to address adherence when initiating treatment (for newly prescribed medicine), but also over the course of treatment through maintenance of appropriate adherence patterns, preventing sub-optimal adherence and changing sub-optimal adherence, once patterns have developed. Interventions targeted at the individual patient level are likely to be

more effective if they address both motivational factors and capacity limitations).

A systematic programme of adherence research across long-term conditions is essential to guide the delivery of recommendations for medicines use within NHS NSFs and address a fundamental inefficiency in healthcare delivery. The potential benefits are likely to include: better care tailored to patient needs, higher rates of adherence to appropriate medicines, fewer unwanted and unused prescriptions, more effective management of long-term conditions, increased patient safety and satisfaction and fewer emergency admissions.

B) Informed choice and shared decision making

Research questions:

1.   What are the most clinically effective and cost-effective ways of communicating the potential benefits and risks of medicines to promote informed choice?

2.   What are the strengths, weaknesses and consequences of different approaches to joint decision-making, seen from the vantage point of various stakeholders (e.g. prescribers, patients, funders)?

Why is this important?

The principles of informed choice and shared decision-making have largely been developed from theoretical and conceptual models. The competencies listed for shared decision- making consist of a number of different skills and patients have shown that they may be valued differently by different people. While the right of patients to be involved in treatment decisions is accepted, the practice of shared decision making may result in practitioners and patients playing different roles than they have to date in health care consultations. This may have implications for responsibility and accountability. Information asymmetries also need to be addressed and this may require structural changes to health services and their delivery. Patient related outcomes need to be included.

C) Support processes: prescribing-related consultations and medicines usage review

Research Questions

1.   How can we enable new and existing prescribers to identify individuals at risk of nonadherence or those who are a priority for medicines review and adherence support. How can we best provide it?

2.   How can practitioners and patients be supported to improve the quality of prescribing-related consultations and medicine use reviews so that they facilitate informed choice and optimal adherence to medicine?

3.   How can we facilitate the open disclosure of medicine-taking behaviours within consultations relating to medicines prescribing and review? How can we equip health practitioners to respond appropriately and effectively?

4.   What are the effects of non-prescriber medicine reviews (e.g. by pharmacists) on patients, prescribers and outcomes? How can the process of medicine review be enhanced or improved to address issues of informed choice and adherence?

Why this is important?

Nonadherence is often a hidden problem. Many patients are reluctant to express doubts and concerns about medicines because they fear that it will displease the practitioner. We need better methods for overcoming this problem and promoting open discussions about medicines and adherence.
 There is a new and growing agenda relating to non-medical prescribers (pharmacists, nurses etc.) This is a key context issue and there are a range of questions relating to patient perspectives on new prescribers and to new and existing prescribers' perceptions and skills. The effects of new prescribers on patient adherence to medicines should be included in any research agendas designed to evaluate new prescribers. The inclusion of formal procedures for medicine review within the pharmacy contract in England provides an opportunity for improved medicine support for patients. We need a better understanding of the effects of non-prescriber medicine review on medicines

usage and outcomes and of how reviews might be improved to benefit patients and society.

D. Overarching issues Groups for special consideration, vulnerable groups

Consideration of vulnerable groups cuts across the above themes and is relevant for all research questions. Work in this area requires systematic reviews of the available literature followed by empirical studies. Specific questions are:

1.   What are the effects of social disadvantage and ethnicity on informed choice, shared decision making and adherence to prescribed medicines?

2.   How do the perceptions and life circumstances of different age groups (children, young adults, elderly people) influence informed choice, shared decision making and adherence. What are the implications for interventions to support these?

3.   What are the particular barriers to medicines use for people with multiple pathologies (and their informal carers) and what interventions are required?

Why this is important

Perceptions of medicines and the value an individual places on sharing decisions with their practitioner have been found to differ by groups such as the elderly and severity of condition. Research into the factors and impact on adherence could inform clinicians and shape clinical care.

1.8   Acknowledgements

All of the stakeholders who took time to comment on the guideline.

1.9   Glossary

Adherence	Adherence – 'the extent to which the patient's behaviour matches agreed recommendations from the prescriber'. Adherence emphasises the need for agreement and that the patient is free to decide whether or not to adhere to the prescriber's recommendation.
Compliance	Compliance – 'the extent to which the patient's behaviour matches the prescribers' recommendations'.
Concordance	Concordance – this is a recent term whose meaning has changed. It was initially applied to the consultation process in which prescriber and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine-taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence
Cost-benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.

Cost-effectiveness analysis	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of additional cost per additional unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes. See also Markov model.
Cost-minimisation analysis	An economic evaluation that finds the least costly alternative therapy after the proposed interventions has been demonstrated to be no worse than its main comparator(s) in terms of effectiveness and toxicity.
Cost-utility analysis	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Decision analysis	A systematic way of reaching decisions, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Decision problem	A clear specification of the interventions, patient populations and outcome measures and perspective adopted in an evaluation, with an explicit justification, relating these to the decision which the analysis is to inform.

Discounting	Costs and benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present. For NICE economic evaluations, health outcomes will be discounted at 3.5% and costs at 3.5% per annum, following the recommendations of the UK Treasury.
Dispensing professional	Professional trained in dispensing medicine, generally a pharmacist or a general practitioner in a dispensing practice
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective. See also extended dominance.
Dosette box	A type of compliance aid. Other terms used are NOMAD, MANRAX and monitored dose system.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Extended dominance	An intervention is extendedly dominated when it can be dominated by a combination of two alternative interventions (i.e. if x% of the population are treated with intervention A, and y% are treated with intervention C where x + y = 100%, the overall result will be an intervention strategy that is both cheaper and more effective than intervention B). See also dominance.

Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
Forgiveness	The ability of a drug to sustain its pharmacological action after a dose has been missed
GDG	Guideline development group who developed the guideline
Health care professional (HCP)	Any health care professional- specialists, general practitioner, pharmacists, nurse prescribers who are involved in the prescribing of medicines, dispensing of medicines or have designated roles e.g. specialist nurses, in the discussion with patients about those medicines.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of healthcare resources.
Health-related quality of life	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Informed adherence	Informed adherence refers to an outcome of informed choice in decision to take medicines and supported adherence

Incremental Cost Effectiveness Ratio (ICER)	The difference in costs between two interventions being compared divided by the difference in effects of the two interventions. For instance, if A and B are being compared, then the ICER would be calculated as
	Costs of B – costs of A divided by effects of B – effects of A
Life-year	A measure of health outcome that shows the number of years of remaining life expectancy.
Life-years gained	Average years of life gained per person as a result of an intervention.
Markov model	A modelling technique used when a greater number of health states needs to be considered. They are particularly useful for disease in which events can occur repeatedly over time.
Medicines	The term medicines is used in the guideline to apply to drug treatments that patients may take orally or self-administer such as creams to the skin and drops.
Medicine review	A face to face meeting between a professional and a patient to discuss the patients medicines and medicine-taking behaviour
Opportunity cost	The opportunity cost of investing in a healthcare intervention is the value of other healthcare programmes that are foregone or displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Persistence	The length of time from initiation to discontinuation of therapy. Persistence is measured in units of time.

Perspective	(or viewpoint): This determines which costs to include. For NICE evaluations the perspective is from the NHS and includes costs to the NHS and Personal Social Services. Costs to other public bodies and to patients and carers may be considered as an additional factor.
Probabilistic sensitivity analysis	Probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Quality adjusted life-years (QALYS)	An index of survival that is adjusted to account for the person's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis, QALYS are calculated by estimating the number of years of life gained from a treatment and weighting each year with a quality-of-life score between zero and one.
Shared Decision Making (SDM)	Shared-decision making (SDM) is described as a model of decision making where information exchange is a two way process in the consultation and both deliberation and decision are made by both health care professional and patient.
Specialist	One who has expertise in a particular field of medicine by virtue of additional training and experience.
Time horizon	The time span used in the NICE appraisal that reflects the period over which the main differences between interventions in health effects and use of healthcare resources are expected to be experienced, and taking into account the limitations of supportive evidence.

Unit-dose packaging	Unit-dose packaging is the packaging of a single dose in a non-reusable container.
Utility	This concept is applied in health care to mean the individual's valuation of their state of well-being deriving from the use of health care interventions. In brief, utility is a measure of the preference for, or desirability of, a specific level of health status or specific health outcome.
Willingness to pay (WTP)	WTP refers to the amount that a decision maker is willing to pay for an additional unit of outcome (e.g. an additional QALY). If the WTP is higher than the ICER, the intervention is cost effective. If not, the intervention is not cost effective.

2   Methods

2.1   Introduction

This chapter sets out in detail the methods used to generate the recommendations for clinical practice that are presented in the subsequent chapters of this guideline. The methods are in accordance with those set out by the Institute in 'The guidelines manual'. April 2007. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidelinesmanual. *The Guideline Development Process – an overview for stakeholders, the public and the NHS* describes how organisations can become involved in the development of a guideline.

2.2   Developing key clinical questions (KCQs)

A series of key questions created from the scope was the first step in the development of the guideline. The key questions formed the starting point for the subsequent evidence reviews and facilitated the development of recommendations by the GDG.

The key questions were developed by the project team with the guidance from the GDG. Where possible, the questions were refined into specific research questions by the project teams to aid literature searching, appraisal and synthesis. However, due to the generic nature of the guideline, full PICO parameters were not applicable to the developed research questions. The full list of key questions is shown in appendix B.

Reviews of the evidence using systematic methods relating to searching and appraisal were conducted to answer the clinical questions in line with The guidelines manual. The GDG and development teams agreed appropriate inclusion and exclusion criteria for each topic area in accordance with the scope.

2.3   Literature search strategy

2.3.1   Scoping search

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: National Library for Health (NLH) Guidelines Finder, National Guidelines Clearinghouse, Scottish Intercollegiate Guidelines Network (SIGN), Guidelines International Network (GIN), Canadian Medical Association (CMA) Infobase (Canadian guidelines), National Health and Medical Research Council (NHMRC) Clinical Practice Guidelines (Australian Guidelines), New Zealand Guidelines Group, BMJ Clinical Evidence, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Heath Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHSEED) National Research Register and Current Controlled Trials.

2.3.2   Evidence review for guideline development

The aim of the evidence review was to identify the most relevant, published evidence in relation to the key clinical questions generated by the GDG. Reviews of the evidence using systematic methods relating to searching and appraisal of the evidence were conducted.

The following bibliographic databases were searched from their inception to the latest date available: Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Database (HTA), MEDLINE, EMBASE, CINAHL, AMED (Allied and Complementary Medicine Database), CENTRAL (Cochrane Controlled Trials Register). When appropriate to the question PsycINFO was also searched.

The search strategies were developed in MEDLINE and then adapted for searching in other bibliographic databases. Systematic reviews and randomised controlled trials were searched for using methodological search filters designed to limit searches to these study designs. These were devised

by the Centre for Reviews and Dissemination and the Cochrane Collaboration. The economic literature was identified by conducting searches in NHS Economic Evaluations Database (NHSEED) and in MEDLINE and EMBASE using an economics search strategy developed by ScHARR at the University of Sheffield.

Databases of the results of the searches for each question or topic area were created using the bibliographic management software Reference Manager.

The search strategies for all questions or topic areas developed for the Medline database are detailed in appendix B. Details of all literature searches for the evidence reviews are available from the NCC-PC. Further references were also suggested by the GDG.

2.3.3 How the evidence reviews were conducted

The research literature relating to shared decision-making and adherence is complex and overlapping. It was decided that individual literature searches for each clinical question would result in a duplication of work as the retrieved evidence would potentially overlap from question to question. Very focused searches would also be likely to miss relevant literature as terminology is not standardised. Broad searches were therefore undertaken to produce evidence reviews on each of the following key topics:

- Shared decision-making in the context of prescribed medicine.
- Barriers to shared decision-making and adherence in the context of prescribed medicine.
- Interventions to enhance adherence in the context of prescribed medicine.

The retrieved evidence was then sifted and allocated to the relevant clinical question.

Additional focused literature searches were undertaken for some of the key clinical questions. The GDG viewed the questions as important in clinical practice and wished to ensure that no important study had been missed out. These were:

- What tools are available to help elicit patients' information needs about medicines?
- What tools are available to help elicit patients' beliefs about medicines?
- How can a practitioner detect whether a patient agrees/disagrees with recommendation to take medicines?
- How can practitioners elicit patient's preferences for involvement in decisions about medicines?
- Do interventions to increase patient involvement increase length of the consultation?
- Does change in dosing regime affect adherence?
- Does medicine formulation/packaging affect adherence?
- What is the effect of prescription charges/costs on adherence to prescribed medicine?
- How can practitioners assess adherence?
- Do medicine reviews increase adherence to prescribed medicine?
- Does the use of multi-compartment medicine systems increase adherence to prescribed medicine? [see chapter 8 for more detail on this question]*

*This review was originally titled 'does the use of dosette boxes increase adherence to prescribed medicine'. The evidence search using a variety of terms returned no studies. After consultation it was brought to our attention that devices like dosette boxes may be classified under different headings and that some researchers label them as 'reminders' or as 'packaging'. We therefore re-examined the papers included in the packaging review and reminder reviews and extracted those relevant to dosette-type devices. The review by Heneghan (2006) and some RCTs/systematic reviews which had been incorrectly placed with the packaging and reminder questions are now relocated to the question. These we have termed multi-compartment medicine systems although there is no agreed term in the published literature. The original search terms matched the terms needed for this restructured

multi-compartment medicine system question.   For example the search terminology included 'dosette', 'nomad' or 'manrax' 'monitored dosage system' and 'compliance aid'.

The specific search strategy for each topic area varied and was agreed with the development team (with input from the GDG as necessary). The review parameters were agreed with the GDG and aimed to provide the best available evidence. For further details on the methodology and inclusion/exclusion criteria please see individual evidence reviews.
The literature on barriers to shared decision-making and medicine taking, shared decision-making and adherence to medicine is not well indexed, therefore, despite the comprehensive and detailed searches, some trials that met our criteria may have been missed.

In line with NICE Equality scheme additional searches of the literature were undertaken to ensure that general searches had located all evidence relevant to vulnerable groups in the United Kingdom[1].

2.4   Identifying the evidence

After the search of titles and abstracts was undertaken, full papers were obtained if they appeared to address the key clinical question. The highest level of evidence was sought. However, other types of quantitative evidence, qualitative evidence and expert formal consensus results were used when randomised controlled trials were not available. Only English language papers were reviewed. Following a critical review of the full text paper, articles not relevant to the subject in question were excluded. Studies that did not report on relevant outcomes were also excluded.

2.5   Critical appraisal of the evidence

From the papers retrieved, the Senior Health Services Research Fellow (SHSRF) and the Health Service Research Fellow (HSRF) synthesized the evidence for each question or questions into a narrative summary. These form the basis of this guideline. Each study was critically appraised using the

---

[1] www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp

Institute's criteria for quality assessment and the information extracted for included studies is given in Appendix C. The content and delivery of interventions was poorly defined in many studies and it was difficult to decide which studies should be included or excluded. The GDG advised on which studies to include and exclude in these circumstances. Background papers, for example those used to describe the concepts used in the guideline, were referenced but not extracted.

2.5.1 Choice of outcomes

When agreeing key clinical questions the GDG discussed the choice of outcomes for each search. A variety of outcomes are currently found in studies on shared decision-making but the outcomes primarily looked at were patient preferences, identification of beliefs and patient agreement to the decision. Any additional information on factors which may have influenced the study results and had an impact on the wider implementation of an intervention, such as participants' age, ethnicity or social status; dropout rates and payments or rewards given to participants, were recorded in the evidence tables considered by the GDG. The primary outcome measure for all the evidence reviews on interventions to increase adherence was adherence. Adherence levels were the outcome also for studies examining medicine review.

2.6 Health Economics methods

Economic evaluation provides a formal comparison of benefits and harms as well as the costs of alternative health programmes. It helps to identify, measure, value and compare costs and consequences of alternative treatment options. These outcomes are usually synthesised in cost-effectiveness (CEA) or cost utility analysis (CUA), which reflect the principle of opportunity costs. For example, if a particular treatment strategy were found to yield little health gain relative to the resources used, then it could be advantageous to re-deploy resources to other activities that yield greater health gain.

To assess the cost-effectiveness of interventions to increase adherence (interventions to increase adherence), we conducted a comprehensive systematic review of the economic literature relating to medicines and nonadherence.

In accordance with the NICE social value judgement the primary criteria applied for an intervention to be considered cost effective were either:

a) The intervention dominated other relevant strategies (that is it is both less costly in terms of resource use and more clinically effective compared with the other relevant alternative strategies); or

b) The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy (or usual care).

2.6.1 Health Economic evidence review methodology

The following information sources were searched:
- Medline (Ovid) (1966-June 2006)
- Embase (1980-June 2006)
- NHS Economic Evaluations Database (NHS EED)
- PsycINFO
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)

The electronic search strategies were developed in Medline and adapted for use with the other information databases. The clinical search strategy was supplemented with economic search terms. Titles and abstracts retrieved were subjected to an inclusion/exclusion criterion and relevant papers were ordered. No criteria for study design were imposed a priori. In this way the searches were not constrained to randomised controlled trials (RCTs) containing formal economic evaluations. Papers included were:
- Full/partial economic evaluations

- Considered patients over 16 years of age

- Written in English, and reported health economic information that could be generalised to UK.

The full papers were critically appraised by a health economist using a standard validated checklist. A general descriptive overview of the studies, their quality, and conclusions was presented and summarised in the form of a narrative review.

Each study was categorised as one of the following types of full economic evaluation: cost-effectiveness analysis, cost-utility analysis (i.e. cost-effectiveness analysis with effectiveness measured in terms of QALYs gained) or cost-minimisation analysis. Other studies which did not provide an overall measure of health gain or attempt to synthesise costs and benefits were categorised as 'cost-consequence analysis.' Such studies were considered partial economic evaluations.

2.6.2   Cost-effectiveness modelling methods

De novo modelling was considered for aspects of medicine taking. However, due to heterogeneity in the population covered by this guideline this was not possible. This is discussed in more detail in Chapter 10.

2.7   *Forming recommendations*

In preparation for each meeting, the narrative and extractions for the questions being discussed were made available to the GDG one week before the scheduled GDG meeting. These documents were available on a closed intranet site and sent by post to those members who requested it.

GDG members were expected to have read the narratives and extractions before attending each meeting. The GDG discussed the evidence at the meeting and agreed evidence statements and recommendations. Any changes were made to the electronic version of the text on a laptop and projected onto a screen until the GDG were satisfied with these.

All work from the meetings was posted on the closed intranet site following the meeting as a matter of record and for referral by the GDG members.

2.8   Areas without evidence and consensus methodology

The table of clinical questions in Appendix B indicates which questions were searched.

In cases where evidence was sparse, the GDG derived the recommendations via informal consensus methods, using extrapolated evidence where appropriate. All details of how the recommendations were derived can be seen in the 'Evidence to recommendations' section of each of the chapters.

2.9   Update

Literature searches were repeated for the initial evidence-based questions at the end of the GDG development process allowing any relevant papers published up until June 2008 to be considered. Only those studies where recommendations needed substantial revisions were added in detail. Future guideline updates will consider evidence published after this cut-off date.

Two years after publication of the guideline, NICE will ask the National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update. If not, the guideline will be considered for update approximately four years after publication

2.10   Consultation

The guideline has been developed in accordance with the Institute's guideline development process. This has included allowing registered stakeholders the opportunity to comment on the scope of the guideline and the draft of the full and short form guideline. In addition, the draft was reviewed by an independent Guideline Review Panel (GRP) established by the Institute.

The comments made by the stakeholders, peer reviewers and the GRP were collated and presented for consideration by the GDG. All comments were

considered systematically by the GDG and the development team recorded the agreed responses.

2.11 Relationships between the guideline and other national guidance

2.11.1 National Service Frameworks

The National Service Framework for Older People (2001) makes specific recommendations for medicine review in older people.

2.11.2 Related NICE Guidance

This guideline differs from most NICE guidelines in that it is not condition specific but makes recommendations on how to involve patients in decisions about medicines. This guidance should be used in conjunction with condition specific NICE guidance which makes recommendations on what treatments are clinically and cost effective.

NICE and the National Patient Safety Agency (NPSA) have recently produced joint guidance on medicines reconciliation when adult patients are admitted to hospital (www.NICE.org.uk/PSG001).

2.11.3 Other national guidance

In formulating recommendations consideration was given to

- *Report of the Committee on Safety of Medicines Working Group on Patient Information' (2005)*
- General Medical Council document, Consent: doctors and patients making decision together.
  http://www.gmc-uk.org/news/articles/Consent_guidance.pdf
- Mental Capacity Act 2005
  http://www.opsi.gov.uk/ACTS/acts2005/pdf/ukpga_20050009_en.pdf
- Disability Discrimination Act 1995
  http://www.opsi.gov.uk/acts/acts1995/plain/ukpga_19950050_en_1

Through review of published guidance, personal contact and commenting on guideline scope, endeavours were made to ensure that boundaries between guidance were clear and advice was consistent.

2.12   Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The NCC-PC disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

2.13   Funding

The National Collaborating Centre for Primary Care was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

3 Principles and concepts used in the development of the guideline

Clinical guidelines generally provide guidance on the management of clinical conditions. To inform the recommendations evidence is sought regarding the benefits and harms, as well as cost of treatments. This guideline seeks to inform patient involvement in decisions about medicines across clinical areas and as such is more interested in patient and health care professional behaviour than evidence for individual treatments. The development of the guideline required the Guideline Development Group (GDG) to engage with topics more usually found in psychological and sociological literature as well as philosophical and legal issues such as rights and duties of patients and professionals. The GDG discussed these issues at length to develop a working consensus which then allowed them to examine the literature and develop recommendations. These discussions are included in the relevant sections of the guideline where they informed recommendations. The GDG also wished to see the principles they used to develop the guideline brought together in one chapter. This chapter brings together those discussions from different parts of the guideline. Some of this content is therefore relevant to individual chapters and rather than repeat the sections we have inserted hyperlinks to this chapter where appropriate.

3.1 Patients' rights to be involved in decisions about medicines

The prescribing of medicines to patients has become a central part of the delivery of modern medical care. Studies and commentaries on medicine-taking by patients have often emphasised the objective health and cost impacts incurred when patients do not take medicine as prescribed [6]. There is an often unstated and perhaps unrecognised assumption that patients should take medicines as suggested by health professionals [7]. While objective health and cost impacts of patients' behaviour in relation to medicines is important, the right of patients to make decisions in regard to their own health is

accepted in modern practice. The approach taken by this guideline is that patients have a right to be involved in decisions about medicines to the extent that they wish and it is the role of health professionals to facilitate and support patients in their involvement in decision-making and to support patients in taking medicine if the decision has been to prescribe.

It is particularly important for people who are known to frequently experience inequalities in health to have their right recognised to be effectively engaged in decision-making e.g. those with learning disabilities, mental health problems and people of black and ethnic minority origin. These individuals must be afforded equal opportunities for healthier outcomes through the effective provision of appropriate access and support. Practitioners must be aware of their legal duties and responsibilities to make *'reasonable adjustments'* in line with the Disability Discrimination Act (2005).

3.2   *What is meant by involving patients in decisions about medicines?*

Early analysis of consultations between healthcare professionals and patients indicated that consultations were primarily led by the health care professional. Bain (1976) [8] a general practitioner, tape-recorded his own consultations to examine what actually happened in consultations and found that he talked at least as much as the patients did. Tuckett and colleagues (1985) [9] found that doctors frequently inhibited patients from asking questions and did little to encourage patients to present their own view. Historically healthcare professionals have had the dominant role in making treatment decisions and these professionals have primarily been medical professionals. Charles and colleagues (1999) [10] outline a number of assumptions on which this dominant role was based: a single best treatment existed and physicians would be well versed in current clinical thinking; physicians would apply this knowledge consistently to all patients and were in best position to evaluate treatment decisions and tradeoffs; and because of their professional concern for the welfare of their patients, physicians had a legitimate interest in each treatment decision. Significant asymmetry between professionals and patients also

existed in terms of education, income and status. The assumptions underlying the dominant role of the professional have been increasingly challenged as both medicine and society changed [11]. More treatments for conditions have become available with complex risk – benefit analyses required. It was recognised that it is the patient who has to live with the consequences of these decisions and might be in a better position than the professional to evaluate and weigh these. Medical practice has also shifted away from acute care towards both chronic long term care and preventative care which requires a long-term commitment to medicines taking and may require frequent monitoring of medicines and illness. The principles of informed consent and informed choice in relation to treatment decisions are now enshrined in law and there is an inherent implication in these that the patient is making a decision in relation to their own healthcare. Previous asymmetries between health professionals and patients in terms of education and access to information have also lessened. Parallel to these developments has been sociological and psychological studies that examined patients' medicine-taking behaviour which provided evidence that patients' decisions were rational and logical when using patients' own understanding (see chapter 5).

The concepts of shared-decision making and patient-centredness are part of the response to the need to recognise the role of the patient in medical encounters and decisions. In the literature shared decision-making (SDM) is described as one model of decision-making. In this model information exchange is a two way process in the consultation and both deliberation and decision are made by both health care professional and patient. This is in contrast to a 'paternalistic' model where information is given to the patient and deliberation and decision are made by the health care professional or an 'informed' model where information is given to the patient and the patient makes the deliberation and decision [10]. Intermediate models are also recognised where decision may be led by the professional or handed to the professional following full sharing of information between both parties. Patient-centredness is an approach to the patient which encompasses the sharing of power and responsibility. Mead and Bower (2000) [12] have described patient-centredness as having 5 dimensions (1) adopting the bio-psychosocial

perspective (this means using biological, psychological and social understandings of disease and illness experience); (2) understanding the patient as person; (3) sharing power and responsibility between the doctor and patient; (4) building a therapeutic alliance and (5) understanding them as a person. Despite the interest in these concepts and an agreement that there is a moral value inherent in them, it is accepted by many working in the area that the operationalisation of these concepts is still evolving [13], [11], [14]. The difficulties relating to how to enact shared decision making include overcoming asymmetry in knowledge and experience between patients and health care professional, the difficulty in recognising a shared decision and what this concept means in terms of responsibility of the clinician.

Current evidence exploring health care professionals' views indicate that they perceive difficulties in implementing SDM. A recent systematic review which examined qualitative and quantitative research on health care professionals' views about implementing SDM identified several perceived barriers (Gravel 2006) [15]. The studies included in the systematic review were primarily qualitative and the vast majority of the practitioners were medical practitioners. The three most commonly perceived barriers were time constraints, lack of applicability to patient characteristics and lack of applicability to the clinical situation.

Thompson (2007) [16] describes the current literature as being primarily derived from the perspective of professionals – policy makers, academics or medical professionals and not from the perspective of patients. Using interviews and focus groups he describes patients' wish for involvement to be dynamic with demand varying according to the need for health care, personal characteristics of the patient and the patient-professional relationship. Wish for involvement is higher in this model when illness is chronic, trust in the professional is low and the patient is active. Demand is lower when illness is acute and serious, the patient passive and trust in the professional is high.

Surveys of patients indicate that when asked patients as a group do ask for increased involvement in healthcare decisions. The Picker Institute (2007) [17] published a report examining patient experience of the NHS between 2002

and 2006. Using the results of 26 national patient surveys they report patients' information needs not being met and patients wanting more involvement in health care decisions. In regard to medicines, patients reported wanting more involvement in medicine choices than they currently receive. The surveys indicate that professionals were giving less information about side effects over the time of the surveys and patients felt that fewer decisions were shared decisions in 2006 than in 2004 and 2005.

The literature on decision-making first evolved in the context of life-threatening diseases such as cancer [11] and included decisions for example as to whether or not to have surgery [18].These were often one-off decisions with major consequences. In the case of medicines the initial involvement in the decision to prescribe a medicine is necessarily followed by ongoing, often daily decisions by patients to continue taking the medicine prescribed. Involving patients in decisions to take medicines concerns not just the decisions made within a consultation but also attention to the ongoing decisions that patients make about their medicines following the consultation with a health care professional.

3.3   *What are we trying to achieve in involving patients in decisions about medicines?*

The outcome that we wish to see from patient involvement is an informed choice by the patient in regard to their use of medicines. The term informed adherence has been used to describe an outcome of informed choice and supported adherence [19]. In this understanding achieving a shared agreement is limited if the patient is then not supported to implement their intentions to take the medicine as recommended. Similarly, stipulating unconditional and unquestioning adherence to prescribers' instructions as our goal is, in most cases, not justified if the patient has not made an informed choice about taking the medicine.

In most cases the patient is free to decide whether to take the treatment or not. However, the healthcare practitioner has a responsibility to help ensure that the choice is an informed one. Informed patient choice, rather than

'compliance' is the desired outcome of the discussion. If the patient decides to accept the prescription, then the aim is to facilitate appropriate adherence to the agreed recommendations for how it should be taken to maximise its efficacy and safety for the individual and optimise benefits and reduce risk.

Facilitating informed choice involves more than the provision of information. Informing should be an active process, which involves more than simply presenting the evidence. It also entails eliciting the patient's beliefs and identifying whether pre-existing beliefs might act as a barrier to an accurate interpretation of the evidence. If the interpretation of information is influenced by misconceptions about the illness and treatment, then the patient's choice may not be 'informed'.

3.4 Roles and responsibilities of patients and health care professionals

Concern has been expressed by practitioners that sharing decisions with patients may conflict with their duty of care to patients or their legal or ethical obligations [20]. While the UK General Medical Council (GMC) (2001)[2] considered one of the key duties of a doctor to 'respect the rights of patients to be fully involved in decisions about their care' for many clinicians there is a legitimate area of concern or indeed of conflict between respect for autonomy of the patient and the duty of beneficence when a clinician feels uncomfortable about a patient's wishes. The GMC (2008)[3] has recently updated guidance for doctors about patient consent which makes explicit the right of competent patients to make decisions about their own healthcare. The guidance emphasises the need for doctors to maximise opportunities and patients abilities to make decisions for themselves and that doctors must respect competent patients' decisions even if they do not agree with them. Doctors do not have to provide a treatment to patients which they believe is not in the patients' interest but must under such circumstances explain their reasons and other options, including a second opinion to the patient. It

---

[2] http://www.gmc-uk.org/publications/annual_reports/review_archive/report2002.pdf
[3] http://www.gmc-uk.org/publications/business_plans/Business_Plan_2008.pdf

remains important however for health care professionals to do their utmost to ensure that patients' choices are informed choices as outlined above.

The Mental Capacity Act (2005) [4] governs the making of decisions for people who lack capacity in England and Wales. Under the Act healthcare professionals are advised that they must work on the presumption that every adult patient has the capacity to make decisions about their care, and to decide whether to agree to, or refuse, an examination, investigation or treatment. A patient is regarded as lacking capacity once it is clear that, having been given all appropriate help and support, they cannot understand, retain, use or weigh-up the information needed to make that decision, or communicate their wishes[5].

Healthcare professionals are advised that assumptions must not be made that a patient lacks capacity to make a decision solely because of their age, disability, appearance, behaviour, medical condition (including mental illness), their beliefs, their apparent inability to communicate, or the fact that they make a decision that health professionals disagree with[6].

Healthcare practitioners need also to consider their obligations to the wider society and cost constraints of the healthcare system in which they work when prescribing.

3.5   *Understanding the influences on medicine-taking by patients*

If health care professionals are to facilitate patient involvement in decisions about medicines it is helpful and necessary to understand how patients approach the taking of medicines, in particular the ongoing appraisal of medicines that continues after a consultation. Investigation into why patients do not take medicines as prescribed indicates that the decision to take medicines and the continuing taking of medicines should be considered as a complex behaviour. Fig 1 indicates a diagrammatic representation of current

---

[4] http://www.opsi.gov.uk/ACTS/acts2005/pdf/ukpga_20050009_en.pdf
[5] http://www.gmc-uk.org/publications/business_plans/Business_Plan_2008.pdf
[6] http://www.gmc-uk.org/publications/business_plans/Business_Plan_2008.pdf

evidence regarding factors and influences on medicine-taking by patients. As the figure shows there are a number of influences on patients. Many of these factors interact and the arrows indicate the dynamic nature of the process.

Internal factors represent the beliefs and experiences of the patient. These include the patient's beliefs about their symptoms or disease, their beliefs about medicines in general and their own reaction to medicines. These will influence their intention to take a medicine as suggested by a health care professional. Even when patients intend to take a medicine they can experience difficulty in doing so because of practical problems such as packaging or complexity of regime or they may forget to take medicines. Patients conduct their own appraisal of the medicine they are taking and evaluate its effects against their own expectations of what the medicine will achieve. This feeds into their beliefs about their medicines which in turn influences their intention to take or not to take the prescribed medicines.

External factors are those that feed into the patient's internal appraisal process. These include communication with family and friends and the communication they have with their health care professionals. Information about medicines will be available from multiple sources including documentation patients get with their medicines, from the pharmacist or dispenser or from any other health care professional the patients comes into contact with. Patients may get information from other patients who have taken the same medicine. Patients may be influenced by the attitude in society to a particular medicine or medicines in general and information may be received from media sources.

The research evidence indicates that patients' decisions about medicines are made within the patients' own frames of reference and make sense within the patients' understanding. Patients however often do not disclose to the health professional any reluctance to take medicines or disagreement with the prescribers recommendation of a prescription or their non-taking of medicines. The onus is on the health professional to elicit and explore patients' beliefs and experiences and facilitate the patient making an informed choice about whether or not to take a prescribed medicine.

When patients do not take medicine as prescribed they may therefore be doing this on an intentional basis i.e. they have made their own appraisal and have decided to take the medicine in their own way or even not at all. This may be done with full information about medicines, illness and consequences of taking or not taking recommended medicine.
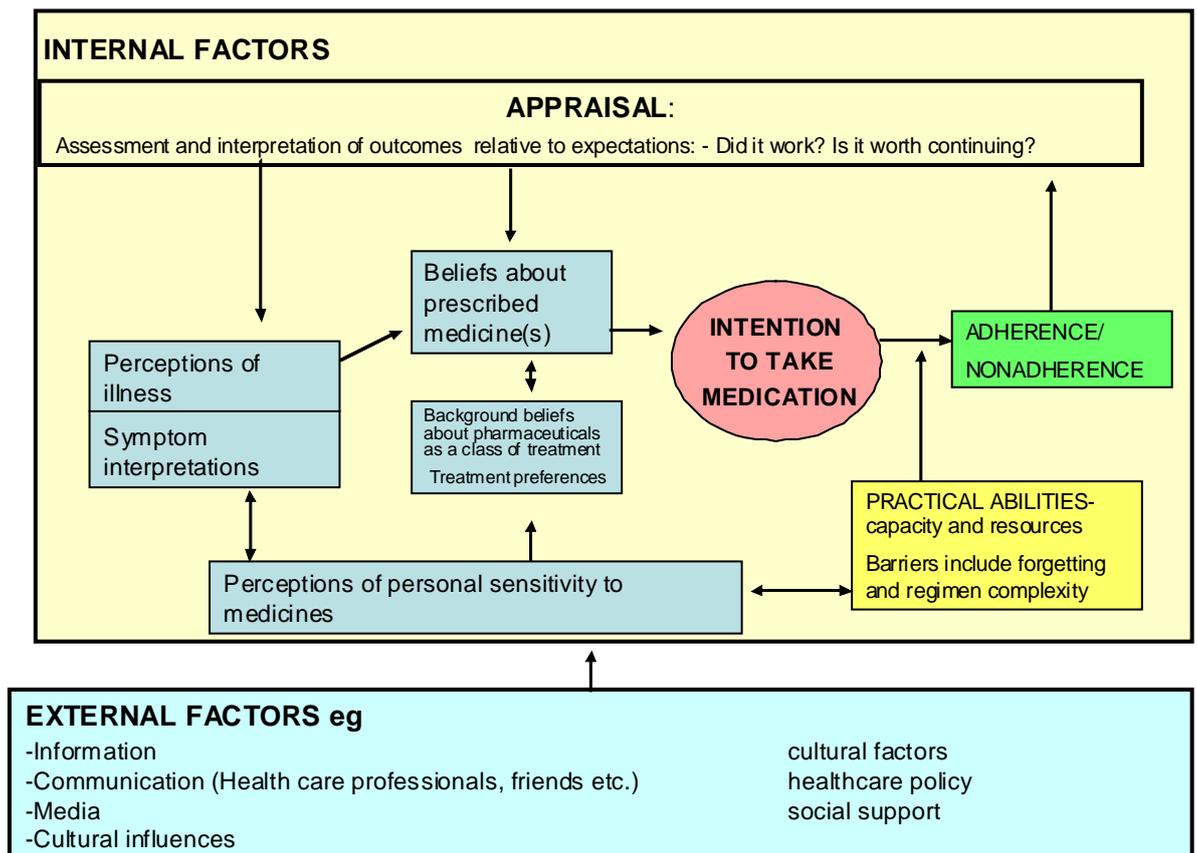
Figure 1. Horne, R. Concordance, Adherence and Compliance in Medicine-Taking. Report for the National Co-ordinating Centre for NHS Service and Delivery Organisation R&D (NCCSDO) (2005), pp 139.

In routine clinical terms the factors included in figure 1 that are barriers to medicine-taking can be considered as either practical barriers or perceptual barriers. Perceptual barriers are ways in which individual patients think about their illness or condition and treatments both in general and specifically. Practical barriers are those such as cost, memory or dexterity that affect individuals' ability to use the medicine recommended to them.

3.6   Terminology and structure of guideline

The terminology used in the area of medicine-taking highlights the changing understanding of medicine-taking behaviour and the changing relationships between health care professionals and patients. The terms compliance, adherence and concordance are now often used interchangeably and inappropriately to describe medicine-taking by patients. The approach taken by this guideline is to use terminology as recommended in the Report for the National Co-ordinating Centre for NHS Service Delivery and Organisation R&D on Concordance, Adherence and Compliance in Medicine-Taking (2005) (NCCSDO) [1].

Compliance has been the most commonly used term in relation to medicine-taking and can be defined as 'the extent to which the patients' behaviour matches the prescriber's recommendations' [21]. The term has been criticised as it is suggested it carries an implicit assumption that it is the prescriber's role to decide on the correct medicine and the patient has a passive role which is to take the medicine as he/she has been instructed. Non-compliance indicates a failure to follow instructions and can be used as a pejorative term indicating a patient who is unwilling to do as instructed by a prescriber who knows what the patient needs.

Adherence is defined as 'the extent to which the patient's behaviour matches agreed recommendations from the prescriber'. Adherence shifts the balance between professional and patient to suggest there should be agreement between prescriber and patient about the prescriber's recommendation. In this understanding adherence is referring to behaviour matching an agreed recommendation but patients may agree to take medicine and yet not take it precisely as prescriber intended. Adherence is not binary.

Concordance is less easily defined and its meaning has changed. It was initially used to describe the consultation process by which agreement about therapeutic decisions was reached by prescribers and patients. It presumed an exploration of patients' views and their incorporation into the decision made. The term therefore addresses consultation processes and does not include any aspects of medicine-taking as do compliance and adherence.

Some uses of the term have included both communication and support for patients in medicine taking. While the term concordance has been useful in drawing attention to the need to engage patients in decisions there is currently no agreed way in which one can judge whether a consultation has been concordant. Concordance does reflect current social values where patients are seen as active participants in their own healthcare but does not address medicine-taking and may or may not lead to improved adherence.

We have chosen to discuss the consultation process regarding medicines separately from actual medicine taking. We use the term 'shared decision-making about medicines' to refer to the healthcare professional–patient/carer consultation and the term adherence to describe patients' medicine-taking behaviour. The guideline has looked separately at evidence about interventions to increase patient involvement in the decision to take medicine within the consultation and at evidence about interventions to support patients in taking of medicines. While this division is useful when examining the literature and making recommendations, the dynamic nature of medicine-taking must not be forgotten. Patients' perceptions and beliefs will change over time and the experience of taking a medicine will also influence patients' intentions to continue taking that medicine and others prescribed.

From a therapeutic perspective concepts of persistence and forgiveness of a medicine are also important. Persistence refers to how long the patient takes the medicine for and forgiveness refers to whether or not medicines will provide some benefit even if not taken all the time at the recommended dosage and timing.

Fig 2 provides a representation of the patient's pathway. The patient comes to the consultation with their own beliefs and experiences (see section 5). In the meeting with the health professional the patient's complaint is assessed and a prescription may be recommended by the health professional. Within the consultation the decision as to whether or not the patient leaves with a prescription may be led completely by the health professional or negotiated between health professional and patient. If the patient leaves the consultation

with a prescription they may or may not take the prescription to be dispensed,
and even if the medicine is dispensed they may or may not take the medicine.
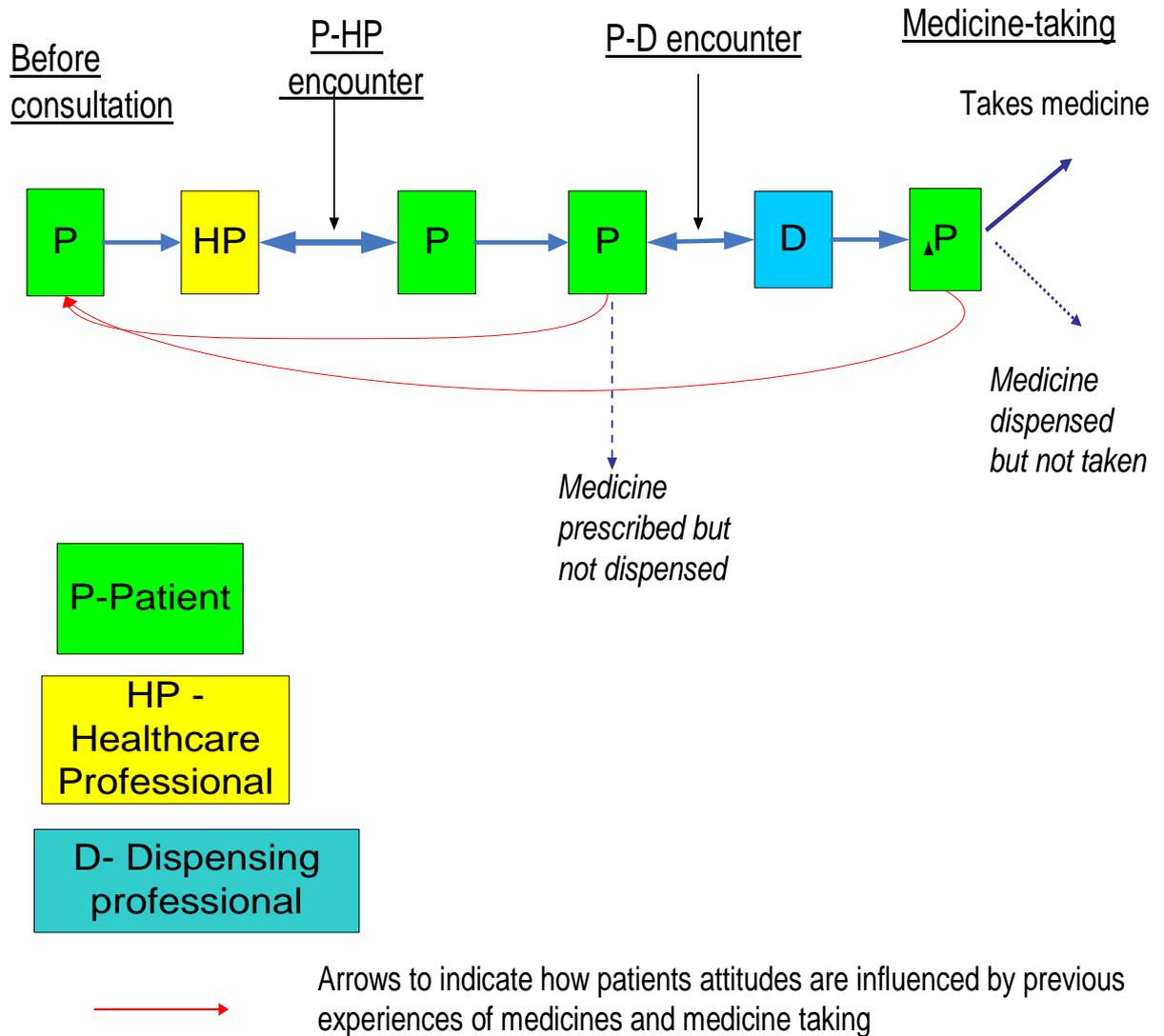
Fig.2 Simplified representation of patient pathway

3.7   *Shared decision-making about medicines*

Models of shared decision-making for use in clinical practice have been
developed. Towle (1997) [22] suggested steps for shared decision-making and
these have been adapted by Elwyn (1999) [23] following exploratory research
with general practitioner registrars. They suggest that population surveys
cannot predict preference of individual patients for involvement and patients'
preferences for involvement may vary according to clinical situation so the

involvement of patients in decision-making has to be explicitly addressed. Neither can patients consider their role in actual making of a decision until they have information about their options and the risks and benefits of those options. The following stages are suggested by Elwyn (1999) to involve patients in healthcare decisions and by implication this also describes the competencies required by practitioners to involve patients (Elwyn 1999) [23].

- Implicit/explicit involvement of patients in decision-making process

- Explore ideas/fears and expectations of problem and treatments

- Portrayal of options

- Identify preferred format and provide information

- Checking process: understanding of information and reactions

- Acceptance of process and role in decision-making

- Make, discuss, or defer decisions

- Arrange follow-up

While these models have been developed when considering a variety of decisions we have used this model to provide an outline structure for our discussion and recommendations about sharing decisions about medicines in consultations. While a treatment can never be understood without reference to the underlying disease, illness or symptom it is beyond the scope of this guideline to make recommendations about general communication and about how diagnosis and prognosis should be explained to patients. These do overlap with our recommendations on communication about medicines but we have not examined these areas explicitly.

Although we have used the term SDM in this guideline and have used literature relating to SDM the understanding of the Guideline Development Group is that this is a process and that we are addressing the 'sharing' of decisions rather than defining what a shared decision is. Edwards (2006) [24]

have suggested that it is the process of involving patients in decisions that delivers benefits for patients rather than attaching importance to defining who makes the decision. Given the difficulties in defining precisely what a shared decision is we cannot advocate that the outcome from this process has to be a 'shared – decision'. For many patients this may be the preferred outcome, other patients will prefer to give the decision to the professionals and others to make their own 'informed' decision. Cox (2007) [25] in a study about prescribing of medicines in general practice, found that 39% of patients wanted the GP to share the decision, 28% wanting the GP to be main decision-maker, 17% wanted the GP to be the only decision-maker, 14% preferred that the patient be the main decision-maker and 2% the only decision-maker. Given the evidence that patient involvement in choices about medicine is lower than desired by patients and that prescribers are not good at recognising which patients want involvement our recommendations aim to make the process of involvement more explicit and to increase overall patient involvement.

4 Interventions to increase shared decision-making about medicines

4.1 Recommendations

[Hyperlink to recommendations section on Patient Involvement in Decisions About Medicines](#)

[Hyperlink to recommendations section Communication Between Healthcare Professionals](#)

4.2 Introduction

Shared decision-making can be broadly defined 'as a decision-making process jointly shared by patients and their health care provider' (Legare 2008) [26]. As discussed in chapter 3 the concept of shared decision-making evolved as a development from a predominantly paternalistic model of professional and patient interactions. Makoul and Clayman (2006) [27] found that the most commonly occurring themes in discussions of concepts of shared decision making were patient values and preferences, options, partnership and patient participation, with 17 other concepts also given considerable weight. In a review of communication about medicines Cox (2004) [28] sets out how patients and professionals need to have two way discussions in which they exchange information and views about medicines.

[Hyperlink to section 3.3 What we are trying to achieve in involving patients in decisions about medicines](#)

4.3 Process of shared decision-making

[Hyperlink to section 3.7 Shared decision-making about medicines](#)

4.4 Methods

Searches were conducted to gather the most relevant evidence relating to the key clinical questions on shared decision-making. Reviews of the evidence using systematic methods relating to searching and appraisal were conducted to answer the clinical questions in line with the NICE Technical Manual. The GDG and project teams agreed appropriate inclusion and exclusion criteria for each topic area in accordance with the scope. Initially an overall search of relevant Randomised Controlled Trials (RCTs) and Systematic Reviews was

conducted using shared decision-making terms. The articles retrieved were then separated under the relevant key clinical questions. Reviews of the evidence using systematic methods relating to searching and appraisal were conducted to answer the clinical questions. However, this did not answer all the Key Clinical Questions succinctly so further searches were done using lower grades of study design.

After the key terms were searched we generated a list of abstracts which were sifted to find relevant articles. Full articles of those deemed to have relevance to the question were obtained. These were then further assessed with regards to our inclusion and exclusion criteria for the question and either included or excluded. We were specifically looking for studies regarding medicine-taking. There is a wide body of evidence relating to decision-making in oncology and surgery but these were excluded.

We extracted the evidence from each included article for study quality, and then brought together the results into an evidence review for each key clinical question. The evidence reviews were structured into explanatory narratives for each article. These were then combined to provide evidence. It was difficult to separate out the content of some of the interventions contained in systematic reviews. For example there was overlap of interventions which explored the improvement of communication between patients and practitioners and interventions exploring those exploring how information should be presented and discussed between practitioners and patients. We have therefore included some studies in more than one section and have indicated this where appropriate.

4.5 Is it possible to increase patient involvement in decisions about medicines?

Related References	Evidence Statements (summary of evidence)
Patient-centred communication in the consultation	
Rao (2007)[29]	One systematic review of how to improve the communication behaviours of physicians and patients found that the interventions studied statistically significantly improved the patient-centred communication behaviours of physicians and residents. Interventions had modest effects in improving patients' communication behaviours. Interventions had modest effects in improving patients' communication behaviours.
Rao (2007)[29]	In one systematic review there was a mix of statistically significant and statistically non-significant results, depending on the communication behaviour studied – e.g. 5/7 found statistically significant changes in patients' communication patterns. All of these included skills practice as part of the intervention, the other 2 studies were low intensity;
Rao (2007)[29]	One systematic review investigated the intensity of interventions and found that higher intervention intensity was clearly related to improvements in physician communications. This was less pronounced for patient communication interventions.
Lewin (2001)[30]	One systematic review found that some interventions

	to promote patient-centred care in consultations led to statistically significant increases in the patient-centredness of the consultation process. They concluded that there is limited and mixed evidence on the effects on health care behaviours or health status.
Patient involvement in the consultation	
Rao (2007) [29]; (Harrington (2004) [31]; Kinnersley (2007) [32]; Loh (2007) [33]	Three systematic reviews found mixed results as to whether or not interventions increased patient involvement in the consultation (described below). One RCT study found an increase in patient participation.
Harrington (2004) [31]	In one systematic review, 10 RCTs found a statistically significant increase in participation, while 5 RCTs found a statistically non-significant increase.
Kinnersley (2007) [32]	In one systematic review patient participation was increased in 8 out of 14 RCT studies and no effect was found in 5 RCT studies.
Wetzels (2007) [34]	One systematic review found limited evidence (three RCTs) of interventions aimed specifically at improving older patients' involvement in consultations.
Wetzels (2007) [34]	Those RCT studies that did investigate older patients' involvement found that the interventions resulted in the patients asking more and different questions, and so they may become more active in consultations due to pre-visit preparation.
Type of behaviour evoked	

Harrington (2004) [31]; Kinnersley (2007) [32]; Wetzels (2007) [34]	Question-asking was the most targeted behaviour found by one systematic review (Harrington, 2004). 5 of the studies found statistically significant increases in this behaviour and 5 studies found statistically non-significant effects (Harrington 2004). In another systematic review (Kinnersley 2007) 6 out of 17 studies found statistically significant increases and the other 11 studies found no statistically significant effects on question-asking. Another systematic review (Wetzels 2007) found one study where more participants asked questions and one study where few prepared questions.
Harrington (2004) [31]	In one systematic review there was a statistically significant increase in clarifying issues.
Harrington (2004) [31]	One systematic review found a statistically significant increase in patients' perception of control over health and for an active role in health care, recall of information, adherence to recommendations, attendance and clinical outcomes.
Harrington (2004) [31]; Kinnersley (2007) [32]; Loh (2007) [33]	One systematic review (Harrington 2004) found a statistically significant increase in satisfaction for only two RCTs however there was high satisfaction found overall. In one systematic review (Kinnersley 2007) 14 out of 23 studies showed no change and 5 had increased satisfaction. In another RCT (Loh 2007) patient satisfaction was statistically significantly higher in the intervention 29.8 (s.d=2.7) than the control group 27.0 (s.d=3.6), p=0.014.
Type of intervention	

Rao (2007) [29]; Harrington (2004) [31]; Kinnersley (2007) [32]; Wetzels (2007) [34]	In 4 systematic reviews most of the interventions were written, e.g. booklet/checklists, while some were videotapes or face to face coaching.
Harrington (2004) [31]; Kinnersley (2007) [32]	One systematic review found that face-to-face and video interventions showed more statistically significant results than written interventions (Harrington 2007). Another systematic review found a small to moderate statistically significant increase for writing alone and coaching.
Wetzels (2005) [35]	One consultation leaflet RCT (including open and pre-structured questions) to improve involvement of older patients, showed an increase in satisfaction but no effect of the leaflet on involvement, enablement or satisfaction. There was a statistically significant result of reporting more psychological symptoms to their GPs.
Little (2004) [36]	One RCT found that a general leaflet which asked patients to list issues they wanted to raise questions led to a statistically significant increase in satisfaction but not in other aspects. The leaflet was statistically significantly more effective when consultations were short. The leaflet increased the number of investigations by the doctor.
Wilkinson (2002) [37]	One RCT of an education guidebook to encourage and support participation found no statistically significant differences in the effectiveness of their primary care visit. There were statistically significant differences for those receiving preventative health care interventions.

Ross (2004) [38]	One RCT found the use of a patient-accessible online medical record found no statistically significant results for self-efficacy, adherence, health status or patient satisfaction. General adherence to medicines advice was statistically significantly improved.
Loh (2007) [33]	One RCT found no statistically significant differences in treatment adherence.

4.5.1 Evidence to recommendations

The GDG were interested in what evidence was available to indicate that patient involvement in decisions about medicines can be increased. The evidence is complex and difficult to interpret because of the lack of standardisation of interventions, the use of multiple interventions in some trials and lack of transparency in reporting of studies. A significant proportion of studies included in systematic reviews were carried out in US settings and the majority of interventions for patients and practitioners were carried out before consultations. The GDG were convinced from the evidence reviews that practitioner skills could be improved and that these improvements as well as some patient interventions did result in increased patient involvement. The GDG considered it important that practitioners were aware that skills could be improved through further training. The GDG considered that the evidence did not allow them to make specific recommendations about how practitioners should increase patient involvement and requested further searches to look at specific aspects of increasing patient involvement.

4.5.2 Methods of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies: Systematic reviews of randomised controlled trials (RCTs) or Randomised controlled trials of interventions involving shared decision-making in the clinical context.

Types of participants: people prescribed medicine for a medical condition.

Duration of studies: no time limit specified.

Types of interventions: any interventions involving shared decision-making in a consultation between a health care professional and patient.

Types of outcome measures: Patient-centred communication in the consultation; consultation process outcomes: patient involvement, question asking, preparedness; patient care outcomes: satisfaction, knowledge, self-efficacy. type of interventions involved and type of information.

It should be noted that the remit of the guideline is for conditions with prescribed medicine and this excludes conditions which require chemotherapy or screening. All RCTs are within this remit, however many of the systematic reviews included populations outside the remit, this is noted where applicable.

4.5.3   Evidence review

The narratives for this question are not grouped because they cover various aspects of the question. The evidence review has been constructed under the above sub-headings of patient-centred communication, patient involvement, type of behaviour, type of intervention and type of information. It should also be noted that RCTs which were included in the systematic review were not narrated separately so as not to duplicate results.

Rao (2007) [29] conducted a systematic review of interventions to enhance communication behaviours among physicians and patients in an outpatient setting. They included RCTs of interventions which were designed to improve the communication behaviours of physicians and patients. The primary outcome was an assessment of the patient-centred verbal communication behaviours. They rated the intensity of the interventions based on how often it was delivered and the personnel involved in the delivery. Thirty-six RCTs met

the inclusion criteria, 18 trained physicians or residents and 15 trained patients, 3 intervened with both. The majority (26 RCTs) were conducted in primary care clinics while 10 were conducted in medical specialty settings. Twenty of the RCTs were conducted in the USA. Half of participants were assessed before and after the physician-patient interaction. Most of the studies were conducted on audiotapes or videotapes and coders were blinded to group assignment. There were a variety of types of physician/resident interventions (e.g. information, feedback, modelling, and practice). Nearly all interventions included written instructions. Some (10 interventions) included videotapes which modelled desirable communication behaviours. Most RCTs showed statistically significant improvements in the communication behaviours of the physicians/residents. The higher intensity interventions resulted in physicians asking more open-ended questions and less biomedical questions than the comparison groups. They were more likely to elicit the patients' concerns they had prior to the visit, and show a more patient-centred communication style overall. There were statistically significant improvements in the information provision to patients. Rao noted that few RCTs (6) checked for patients' understanding of the information received. 18 studies intervened with patients and showed modest effects. Most of the RCTs were informational (17), often written. In some instances the written information included models of desirable communication with examples of questions to ask (8). Eight RCTs included practicing or coaching sessions and four were feedback. Six interventions were moderately-intense, 2 were rated as high-intensity.

Seventeen of the RCTs used different measures of patient involvement. Seven assessed the degree to which patients spoke during the visit, 5 (moderate intensity interventions) of these showed statistically significant changes in communication patterns. All of these RCTs were skills practice interventions. The other two RCTs interventions were low-intensity and showed no statistically significant results. To conclude, the interventions enhanced communication behaviours with physicians compared to controls and there were modest effects with the patient interventions. Intervention

intensity had a clear relationship to improving the physicians' behaviours but this was follow suit for the patient interventions.

Harrington (2004) [31] conducted a systematic review which looked at interventions to increase patients' participation in medical consultations. There was a mix of populations including primary care and outpatient oncology patients. The inclusion criteria for the review included interventions designed to improve patients' communication with doctors in any setting; and RCTs reporting on the impact of the intervention on the patients' communication. Most of the studies were RCTs, with the others being quasi-experimental. Twenty five papers were retrieved from the search. Most of the studies were from the USA, 2 from Australia, 5 from the UK and one from the Netherlands. Most of the interventions were written followed by face-to-face coaching and videotape. Written interventions were in booklet or checklist form. The specific behaviours most encouraged were question-asking, raising concerns and requesting clarification or checking understanding. The process of communication was measured mostly using interaction analysis from audio recordings. Researchers coding the interactions were blinded in only six of the studies. Overall the effect of interventions was that they encouraged patients to be more active in their consultations. Of the 16 studies examining variables of participation, 10 reported a statistically significant increase and five reported a statistically non-significant increase. All but one of the six face-to-face interventions and all of the video interventions reported statistically significant results in increasing participation. Of the 10 written interventions, only two reported a statistically significant increase. Question-asking was equal in statistically significant increases and statistically non-significant trends. There was a statistically significant increase in requesting clarification on matters. There was no statistically significant increase in satisfaction due to the interventions apart from in two studies. There was overall a high level of satisfaction reported. There was a statistically significant increase in perception of control over health and preferences for an active role in health care, recall of information, adherence to recommendations, attendance and clinical outcomes.

Lewis, Butow, Ford, Street and Brown were studies with cancer patients exclusively.

Kinnersley (2007) [32] conducted a Cochrane review of the effects of interventions before consultations designed to help patients address their information needs. The settings and populations varied, but most were conducted in the USA. The author's stated that this review complemented other Cochrane reviews by Wetzels (2007) [34] and Lewin (2001) [30]. The inclusion criteria was RCTs of interventions which were intended to help the patients, representatives or carers address their information needs in a consultation. This was done by encouraging question-asking, expression of information needs, overcoming barriers to communication and clarifying understanding of the information provided. Outcome measures included the consultation process, consultation outcomes and service outcomes. Thirty-three trials described in 35 studies met the inclusion criteria. Of the studies that assessed single interventions for patients,15 included written materials and four included coaching. Of the multiple component single interventions studies, 4 had coaching and written materials. Results: 17 studies measured question-asking and 6 found statistically significant increases and 11 studies found no effects on the intervention group compared to the control group. Patient participation was measured in 14 studies, it was increased in 8, and had no effect in five studies. Patient satisfaction was measured in 23 studies, in 14 studies there were no changes and in 5 there was increased satisfaction. Patient knowledge was measured in 5 studies, with a reduction in two studies and no changes in 3 studies. According to type of intervention, comparisons between written alone and coaching alone showed similar, small to moderate and statistically significant increases for both types of question-asking. Patient satisfaction was borderline statistically significant for written materials, and the effect of coaching was small and statistically significant. Written materials led to a small and statistically significant increase in consultation length. Coaching also showed an increase but this was not statistically significant. Interventions immediately before the consultation led to a small statistically significant increase in consultation length and patient satisfaction.

It should be noted that many of the studies were from other settings: Brown (1999, 2001), Bruera (2003), Butow (1994, 2004), Davison (1997, 2002), Ford (1995), Oliver (2001) were cancer studies. Finney (1990), Kim (2003), Lewis (1991) were from paediatric and family planning settings.

Wetzels (2007) [34] conducted a Cochrane review assessing the effects of interventions in primary care to improve older patients' involvement. The inclusion criteria included RCTs and quasi-randomised trials; older participants (65 years or over) in primary care; interventions either before during or after the consultation and the interventions had to aim to improve the patients' involvement. Studies with other health care professionals were excluded. The outcome measures included use of health care, preparation for contact with a care provider, contact with the care provider (communication), feedback of care, health status and behaviour, treatment outcomes and outcomes related to health professionals. Three studies met all inclusion criteria (Cegala 2001, Kimberlin 2001 and Tennstedt 2001). They were published in English and conducted in the USA. The interventions were either face-to-face sessions to coach patients in question-asking and participating in consultations (given before the consultation) or they were written interventions (booklet or checklist). The primary outcome measure in two of the studies was the questioning behaviour of patients, while the other study's was self-reported active behaviour. The studies used mostly qualitative analysis to assess the outcomes and these were not assessed at a later date. In Cegala (2001) the trained patients asked more medically-related questions, gained more information and provided more information than control patients. They did not verify information more than control patients and appointment length was not longer overall. In Kimberlin (2001) there was more question-asking about their medicine in the intervention group than the control group. Tennstedt (2000) found older patients were generally not involved in their GP visit. Few prepared questions or identified issues to discuss with their GP. However, only 21% found that the GP dominated the visit. The intervention group reported more active behaviours such as bringing a list of problems to the visit (statistically non-significant in intention to treat analysis but

statistically significant in those who did attend, and higher satisfaction with the interpersonal aspects of the encounter).

In conclusion, there is little evidence of interventions which specifically aim to improve older patients' involvement and thus they cannot recommend the use of the examined interventions in clinical practice. The interventions that were included resulted in patients asking more and different questions, and they became more active in consultations due to pre-visit preparation.

Wetzels (2005) [35] ran a cluster-randomised trial to assess a consultation leaflet implementation programme in which GPs and older patients were encouraged to improve older patients involvement when visiting their GP. This study was conducted in the Netherlands. All patients aged 70 years or above in the intervention practices received a consultation leaflet by mail. This leaflet included a short motivating text on patient involvement and a mixture of open and pre-structured questions to help patients prepare for the next consultation and prioritise which problems they wanted to discuss with their GP. The questions were chosen because they would help to explore patient's ideas, fears and expectations, and they encouraged them to address important issues. At pre-intervention 315 patients, and 263 patients at post-intervention, were included in the study.

Based on results from a previous qualitative study, the authors concluded that it would be important to include GPs in the implementation of patient involvement, so GPs in the intervention group received a 30 minute practice visit to motivate them to involve patients and instructed them in the use of the consultation leaflet.

The main results reported that subjects were satisfied with their involvement and the GP's behaviour during the consultation. However, there was no difference in effect as a result of the leaflet on involvement, enablement or satisfaction between the intervention and the control group. The intervention group leaflet users reported more psychological symptoms to their GP compared with non-users of the leaflet (p=0.034). Overall the main findings do not support the use of the implementation programme on improving involvement, enablement or satisfaction of older patients in their care.

Lewin (2001) [30] conducted a Cochrane review of interventions to promote a patient-centred approach in clinical consultations. The inclusion criteria included RCTs and controlled before and after studies. The interventions promoted patient-centred care in clinical health care consultations, not in social support or social care. Other exclusion criteria included studies that considered cultural, disability, sexuality or other sensitivity training only for health care providers; evaluating training in psychotherapy or counselling for health care providers; studies that trained health care providers to deliver a specific, secondary intervention. The outcome measures included consultation processes; other health care behaviour; health status and wellbeing including physiological measures; patient and/or carers' satisfaction with care. Interventions were grouped into the intensity of patient-centredness and teaching tactics (weak, medium and strong). Five thousand two hundred and sixty titles and abstracts were found, 135 with potential to be included, 17 were included. The studies were mainly conducted in North America; others were from the UK, Switzerland, Norway and Trinidad and Tobago. The aims, format, content of interventions and the clinical conditions on which they focused showed heterogeneity. Studies were grouped into broadly similar interventions: patient-centred training compared with no training for providers (11 studies*); patient-centred training for providers plus patient-centred training or materials for patients (3 studies**); patient-centred training for providers plus condition or behaviour-specific training or materials for providers and patients (2 studies***); patient-centred training for providers, patient-centred materials for patients plus condition- or behaviour-specific materials for providers and patients compared with condition- or behaviour-specific materials for both providers and patients (1 study****). The participants were mainly health care primary care physicians and patients were the recipients in six studies. In some of the studies the primary goal was to increase patient-centredness of care and these studies tended to focus on communication skills as important on their own right, while in other studies patient-centred care was seen as a method to change patient behaviour or improve the health outcome. Overall there is fairly strong evidence that some

interventions which promote patient-centred care in the consultation can lead to significant increases in the patient-centredness of the consultation process.

The following studies dealt with either specific populations or topics outside our main focus: Clark (1998) paediatric doctors, Cope (1986) CCT, Langewitz (1998) paediatric doctors, Lewis (1991) paediatric residents and fellows, Meland (1997) was lifestyle changes for CHD risk.

*Cope (1986), Howe (1996), Langewitz (1998), Levinson (1993), Putnam (1988), Robbins (1979), Roter (1995), Roter (1998), Smith (1995), Smith (1998), Thom (1999).**Joos (1996), Lewis (1991), Pill (1998).***Clark (1998), Meland (1997).****Kinmonth (1998).

Little (2004) [36] conducted a randomised controlled trial to assess the effect of leaflets on empowering patients in primary care consultations. Six hundred and thirty six patients were recruited in the study, aging from 16-80 years and were attendees at one of five general practices in the UK. Participants were randomised to four conditions: receipt of a general leaflet, depression leaflet, both leaflets and no leaflets (control group). The general leaflet encouraged patients to list any issues, to ask questions, talk and discuss any problems of concern with their GP. The depression leaflet listed symptoms of depression (without labelling as such) and asked the patient if they had these, and explained that the doctor would like to discuss them. The outcomes measured were patient satisfaction (the scores reflected aspects of doctor patient communication), consultation time, prescribing, referral and investigation. The only statistically significant interaction was the increase in satisfaction for those who received the general leaflet, the mean difference was 0.17 (95% CI 0.01 to 0.32, p=0.04). Consultation time and the general leaflet were statistically significantly associated with improved satisfaction. The leaflet was statistically significantly more effective when consultations were short (leaflet 0.64, 95% CI 0.19 to 1.08; time 0.31, 0.0 to 0.06. Interactions between both showed those consultations of 5, 8, and 10 minute increased satisfaction by 14%, 10% and 7%. This was also shown for subscales of satisfaction – comfort from communication 1.02 (95% CI 0.36 to 1.68), relief of distress 0.74 (95% CI 0.0 to 1.49), intention to comply with management decisions 0.65

(95% CI 0.06 to 1.23) and rapport 0.81 (95% CI 0.16 to 1.45). The general leaflet increased the number of investigations by the GP (OR 1.43, 95% CI 1.00 to 2.05), which was unlikely to be due to chance or confounders after controlling.

Wilkinson (2002) [37] conducted a randomised controlled trial to investigate the relationship between providing patients with an education guidebook (designed to encourage and support participation in the health care visit) and selected patient and system outcome measures. The study population included 277 predominantly male participants, with an average age of approximately 60 years. This study was conducted in the USA.
Patients in the intervention group were mailed the appointment guidebook with instructions prior to a scheduled routine visit with their primary care provider. The control group was mailed the standard letter informing them of their upcoming appointments. After the visit, the patients in both groups were sent a short questionnaire with instructions and a postage-paid return envelope.
No statistically significant differences were reported in the proportion of patients in the two groups that agreed with any of the six statements, which were relevant to primary care visit effectiveness. However, statistically significant differences were reported in the proportion of patients who received preventative health care interventions of influenza vaccination, pneumococcal vaccination and gender specific cancer screening.

Ross (2004) [38] conducted a randomised controlled trial that assessed the effects of a patient-accessible online medical record on patient satisfaction, adherence and health status in a randomised controlled trial conducted in the USA. The version used in the study, System Providing Patients Access to Records Online (SPPARO) provides access to clinical notes and test results, and also provides a method of sending electronic messages to the clinical staff. Patients included in the study were aged 18 years or older. One hundred and seven were enrolled in the study.

Participants in the SPPARO group were given a user identification and password to SPPARO and a written user guide to the system. The control group continued to receive standard care in practice. Periodic messages were sent by research staff to all participants and they were informed about upcoming surveys and encouraged to contact the research assistant if they had a change of address or telephone number. They were also reminded that they could contact the research assistant if they had problems using SPPARO.

No statistically significant results were found for self-efficacy, adherence to medicines, health status and patient satisfaction. General adherence to medicines advice showed a statistically significant improvement in the intervention group compared with the control group. At 6 months the difference was 2.3 (95% CI -3.7 to 8.3) and at 12 months 7.4 (95% CI 1.8 to 10.9), p=0.01, p=0.02 when adjusted for multiple comparisons. Although the number of patients who visited the emergency department did not differ significantly statistically, there was a statistically significant increase in the number of overall emergency department visits in the intervention group compared to the control group.

Loh (2007) [33] conducted a randomised controlled trial that investigated the effects of a shared decision-making intervention in primary care of depression compared to usual care on adherence, satisfaction and clinical outcomes. The study was conducted in Sudbagen, Germany with primary care physicians as the unit of randomisation. The sampling frame (n=148) were sent a letter and 30 accepted the invitation to take part. Twenty were randomly assigned to the intervention group and 10 to the control group, after drop-out 15 and 8 were left respectively. The physicians had to recruit newly diagnosed depressive patients. The intervention physicians enrolled 263 patients and the control group enrolled 142. After their diagnosis the patients completed a questionnaire measuring patient involvement, depression severity and socio-demographic characteristics. After 6-8 weeks the patients completed a second questionnaire measuring adherence and treatment outcome. At the same time, the physicians rated their assessment of the patients' adherence. The shared decision-making intervention was then implemented with the

intervention group. The intervention was a multi-faceted program including physician training; a decision board for use during the consultation; and printed patient information with specific encouragement to be active in the decision-making process. The physicians in the intervention group completed modules on guideline-concordant depression care. This included enhancing physicians' skills for improving the shared decision-making process. The outcomes measures were patient participation, treatment adherence, patient satisfaction, consultation time and clinical outcomes.

There was no difference in patient participation before the intervention compared to afterwards in the control group, whereas the intervention group had statistically significantly higher patient participation from pre to post intervention (on the doctor facilitation scale, $p=0.001$ and patient participation scale, $p=0.010$). There was no statistically significant difference for treatment adherence. Patient satisfaction was statistically significantly higher in the intervention 29.8 (s.d=2.7) than the control group 27.0 (s.d=3.6), $p=0.014$. There were no values taken for satisfaction before the intervention. There was no difference between groups for length of consultation. Neither group had a statistically significant reduction in depression severity from baseline to post-intervention.

4.6 How can practitioners elicit patients' preferences for involvement in decisions about medicines?

Related references	Evidence statements (summary of evidence)
	No tools designed for use in clinical practice were found.
Ende (1989) [39]; Langewitz (2006) [40]; Tortolero (2006) [41]; Neame (2005) [42]; Braman (2004) [43]; Doherty (2005) [44]; Schneider (2007) [45]; Hill (2006) [46]	The Autonomy Preference Index (API) and developments of the API have been created to elicit patients' preferences for involvement in decision-making and may be reduced to a 6-item subscale.
Cox (2007) [25]	A brief pre-consultation questionnaire may be used to elicit patients' preferences for involvement in decisions about medicines.
Caress (1997) [47]	A set of 5 sort cards can be used to elicit the patients' preferred role and perceived role within the consultation.
Doherty (2005) [44] within a hospital and Cox (2007) [25] before and after a general practice consultation.	Two of these tools have been used within routine clinical settings, but only by dedicated researchers.

4.6.1 Evidence to recommendations

The GDG had requested a specific literature search for clinical tools. No tools for use in clinical practice were found which could elicit patients' preferences for involvement. No clinical tools were found. Two of the shorter research tools had been used in routine clinical settings but by dedicated researchers.

The GDG did not consider it appropriate to recommend these tools outside research settings. The GDG used the evidence from the literature and their professional opinion to develop recommendations on eliciting patients' information needs. The GDG did not consider it could make a specific recommendation on how practitioners should elicit patients' preferences for involvement but noted that the language used in simpler research tools was relatively straightforward. The GDG considered that healthcare professionals needed to be alert to non-verbal clues from patients about their involvement and decisions in the consultation.

4.6.2 Methods of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies – A previous search included only randomised controlled trials (RCTs) and systematic reviews (SRs). No studies which met the criteria were found. We widened the search to include any type of studies to find relevant information to meet our inclusion criteria.

Types of participants - people prescribed medicines for a medical condition.

Duration of studies – no time limit specified for the studies.

Types of interventions - Any intervention (tool) which elicits patient preferences for involvement in decisions about medicines. The tools had to be brief enough to be utilised within a consultation between the patient and practitioner. Therefore long questionnaires were excluded as they would not be manageable.

Types of outcome measures – Any outcome relating to the use of the tool was acceptable as we were looking for a tool which could be utilised within a consultation, rather than looking for specific clinical outcomes.

4.6.3 Evidence review

No tools designed for use in clinical practice were found.

The tools in this review are research tools and not clinical tools designed for use in a consultation. We have included these research studies to illustrate brief questionnaires that have been used in research settings indicating the content of the questionnaires to inform the GDG. We have not reported in detail on development or validation of these questionnaires.

Ende (1989) [39] constructed an instrument to measure patient preferences for making medical decisions and their desire to be informed. The instrument, named the Autonomy Preference Index (API) has a questionnaire format and the scales were developed by a group of 13 clinicians, medical sociologists, and ethicists who were interested in patient autonomy. Items on the scales were tested for reliability and validity. The final API consisted of an 8-item scale on information-seeking and a 15-item scale on decision-making. Within this 15-item scale was a 6-item sub-scale which related to general items. The other 9-items were related to three clinical vignettes and were too disease-specific to be useful for this question. The 6-item scale (part A) meets our criteria (see above) but is a research tool rather than a clinical tool.

The Decision making preference scale (Part A): (responses on a 5-point Likert scale ranging from 'strongly disagree' to 'strongly agree'). The higher the score on the scale, the more patients wished to participate in the decision-making:
1.* The important medical decisions should be made by your doctor, not by you.
2. You should go along with your doctor's advice even if you disagree with it.
3.* When hospitalised, you should *not* be making decisions about your own care.
4. You should feel free to make decisions about everyday medical problems.
5.* If you were sick, as your illness became worse you would want your doctor to take greater control.
6. You should decide how frequently you need a check-up.
* Scoring for these items was reversed, and goes from 5 to 1, rather than 1 to 5.

The API was used within a variety of studies: **Langewitz (2006)** [40]; **Tortolero (2006)** [41]; **Neame (2005)** [42]; **Braman (2004)** [43]; **Schneider (2007)** [45] **and Hill (2006)** [46]. All of the studies used the 6-item subscale as illustrated above, except for Langewitz (2006) [40] who adapted the instrument into two questions and Hill (2006) [46] who adapted the questionnaire slightly to apply to psychiatric patients. Most of the studies posted their questionnaires to the participants rather than having them completed in a clinical setting.

Langewitz (2006) [40]

As part of the questionnaire, Langewitz (2006) [40] adapted the API to 4 point Likert scale: fully agree, slightly agree, slightly disagree, fully disagree.
How much do you agree with the following statements?

- One should stick to the physician's advice even if one is not fully convinced of his ideas (follow physician's advice)
- It should completely be left to physicians to decide on a patient's treatment (Physician should decide)

This was conducted at the University of Basel in Switzerland and was sent to the patients after discharge from hospital.

Degner (1992) [48] adapted the API and placed the questions on sort cards for use with patients with cancer. Their questions were adapted by **Caress (1997)** [47], **Doherty (2005)** [44] and **Cox (2007)** [25].

Caress (1997) [47] conducted a cross-sectional study at a regional renal unit in the North of England with 462 participants from a convenience sample over a 12 month period. 155 of the patients were pre-dialysis, 103 were dialysis patients and 147 were transplant patients. Using a set of sort cards, as used by Degner (1992) [48], the patients picked a single card which was closest to their preferred role in decision-making and also picked a single card closest to their perceived role in decision-making. Patients were also asked to give their rationale for their preferred role.
The 5 sort cards:

Active options

Card A: I prefer to make the final decision about which treatment I will receive.

Card B: I prefer to make the final selection of my treatment after seriously considering my doctor's opinion.

Collaborative option

Card C: I prefer that my doctor and I share responsibility for deciding which treatment is best for me.

Passive options

Card D: I prefer that my doctor makes the final decision about which treatment will be used but seriously considers my opinion.

Card E: I prefer to leave all decisions regarding my treatment to my doctor.

The key points found from the study were that: participation preference was highly individualistic, with a lot of patients wishing to remain passive. Those who did prefer an active role were unlikely to attain this preference; trust in the HCP can influence the preference; desire for information is not synonymous with desire for participation.

Doherty (2005) [44] used the adapted questionnaire to use in an acute hospital trust in England and was one study which tried to elicit the patients' responses within an actual clinical situation.

Cox (2007) [25] included 479 patients who were approached in the waiting room in general practitioner surgeries to participate. They were given an interview where they completed the pre-consultation questionnaire and were also administered a questionnaire after the consultation. The GP was given a questionnaire before, which included their preferred role in decision-making with patients and a questionnaire afterwards detailing their perceptions of the decision-making during each consultation. The doctors' assessment of patients' preference to be involved in shared decision-making was correct in 32% of the consultations, overestimated in 45% of the consultations and

underestimated in 23% of the consultations. The patients' preferences for decision-making involved: 39% wanting the GP to share the decision, 45% wanting the GP to be the main (28%) or only (17%) decision-maker and 16% wanting to be the main (14%) or only (2%) decision-maker.

The questionnaire given to the patients at pre-consultation included the following 5 statements, of which patients were asked to choose one:

- I would prefer that I make the decision about medicines I take for this problem.

- I would prefer that I make the final decision about medicines I take for this problem after seriously considering my doctor's opinion.

- I would prefer that my doctor and I share responsibility for deciding about medicines I take for this problem.

- I would prefer that my doctor makes the final decision about medicines I take for this problem, but seriously considers my opinion.

- I would prefer that my doctor makes all decisions about medicines I take for this problem.

4.7 *What tools are available to help elicit patients' beliefs about medicines?*

Related references	Evidence statements (summary of evidence)
Hamilton (2007) [49]	One RCT that assessed a patient self-completion agenda form on prescribing and adherence showed no statistically significant results for prescription, satisfaction scores or adherence.
Horne (1999) [50]; Menckeberg (2008) [51]; Horne (2007) [52]; Brown (2005) [53]; Khanderia (2008) [54]; Kumar (2008) [55]; Kemp (2007) [56]; Aikens (2008) [57]; Clifford (2008) [58]; Jenkins (2003) [59]; Theunissen (2003) [60]	No tools designed for use in clinical practice were found. The Beliefs about Medicines (BMQ) – Specific component is a research tool which is used to elicit beliefs about medicines.

4.7.1 Evidence to recommendations

No tools designed for use in clinical practice were found although the GDG were aware of current studies to develop such tools, in particular studies seeking to adapt the BMQ for clinical use. The GDG reviewed the research tools found but did not consider it appropriate to use these outside their research settings. The GDG used the information from the research studies and their professional opinion to make recommendations in relation to elicitation of patients' beliefs about medicines. The evidence review of patients' experience about medicines (chapter 5) was used to inform the content of the recommendations about exploring patients' beliefs and concerns.

4.7.2 Methods of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies – we initially included only randomised controlled trials (RCTs) and systematic reviews (SRs), however none of these types of studies were found that met the criteria. We increased the current search to include any type of study in order to find relevant information to meet our inclusion criteria.

Types of participants - people prescribed medicines for a medical condition.

Duration of studies – no time limit specified for studies.

Types of interventions - any intervention (tool) which elicits patient beliefs about their medicines. The tools had to be brief enough to be utilised within a consultation between the patient and practitioner. Therefore long questionnaires were excluded as they would not be manageable.

Types of outcome measures – any outcome relating to the use of the tool was acceptable as we were looking for a tool which could be utilised within a consultation, rather than looking for specific clinical outcomes.

4.7.3 Evidence review

No tools designed to elicit patients' beliefs about medicines for use in clinical practice were found. The tools which we found in this review were research tools. We decided to include studies which used these research tools to illustrate some questions that could be asked to the patient in a consultation. Most studies were in questionnaire form and so we included those which were shortest. We have not reported the parts of the questionnaire which were not relevant to the clinical question.

Horne (1999) [50] created a questionnaire which explicitly states the intention of assessing patients' beliefs about medicines. The beliefs about medicines questionnaire (BMQ) included two parts – the BMQ-General, which assessed beliefs about medicines in general and the BMQ-Specific, which looks at patients' specific beliefs towards their medicine. The study states that the two sections of the BMQ can be used together or separately. As the BMQ-Specific answers the question, and we are looking for brevity within the consultation, this part of the study is reported.

The BMQ-Specific includes two 5-item factors which assess beliefs of the necessity of medicines prescribed (Specific-Necessity) and concerns about medicines prescribed, based on beliefs of the danger of dependence, long-term toxicity and the disruptive effects of medicines (Specific-Concerns).

The BMQ-Specific items, which are rated 'strongly agree, agree, uncertain, disagree or strongly disagree':

- My health, at present, depends on my medicines.
- Having to take medicines worries me.
- My life would be impossible without my medicines.
- Without my medicines I would be very ill.
- I sometimes worry about long-term effects of my medicines.
- My medicines are a mystery to me.
- My health in the future will depend on my medicines.
- My medicines disrupt my life.
- I sometimes worry about becoming too dependent on my medicines.

- My medicines protect me from becoming worse.

The BMQ-Specific was used in many other studies to assess beliefs about medicines for a range of conditions (Menckeberg, 2008 [51]; Horne, 2007 [52]; Brown 2005 [53]; Khanderia, 2008 [54]; Kumar, 2008 [55]; Kemp, 2007 [56]; Aikens 2008 [57]; Clifford, 2008 [58]; Jenkins, 2003 [59]; Theunissen, 2003 [60]).

We did retrieve one study, **Hamilton (2006) [49]**, which was a randomised controlled trial conducted to test the effect of patient self-completion agenda forms on prescribing and adherence in general practice. This RCT was considered relevant as one of the items of the self-completion form was related to expectations of medicines and it was considered a clinical tool.

1610 patients at 10 general practices in Devon and Dorset (UK) were involved in the trial for up to 12 weeks. All patients were given a letter and an envelope when attending their GP. Half the group received an agenda form which they could fill out while waiting for the doctor. The other half received usual care. The agenda form called the SCAF (self completion agenda form) included five questions:

1. What made you decide to come to see the doctor? Please describe the problem you have e.g. symptoms or current illness.

2. Your ideas about your illness: what do you think is wrong with you?

3. Your concerns: have you any particular worries about your illness?

4. Your expectations: how do you think your problem should be treated? What do you hope the doctor will do?

5. Do you think you should receive a prescription for your problem?

The GP was handed this form when the patient went into their appointment, to use in whichever way they thought appropriate. There were no statistically significant differences between proportion of patients who received a prescription, or in satisfaction scores or adherence to prescribed medicines.

4.8 What tools are available to help elicit patients' information needs?

Related references	Evidence statements (summary of evidence)
	No tools designed for use in clinical practice were found.
Kinnersley (2007) [32]	One systematic review found that 17 RCTs measured question asking with 6 finding statistically significant increases and 11 finding no effects.
Kinnersley (2007) [32]	One systematic review found that patient satisfaction in 14 RCTs showed no changes but in 5 RCTs there were statistically significant increases in satisfaction.
Strydom (2001) [61]	One questionnaire has been developed which can assess information needs of people with learning disabilities.
Agård (2004) [62]	One study used 4 open-ended questions to elicit patient's information needs.
Duggan (2000) [63]; Astrom (2000) [64]; Zwaenepoel (2005) [65]	Three studies included 5 open questions from the Intrinsic Desire for Information (IDI) scale which can elicit information needs from patients.
Ende (1989) [39]; Langewitz (2006) [40]; Tortolero (2006) [41]; Neame (2005) [42]; Braman (2004) [43]; Doherty (2005) [44]; Schneider (2007) [45]	Seven studies use the Autonomy Preference Index 8-item scale to elicit the information needs of patients.

4.8.1 Evidence to recommendations

No tools validated for use in clinical practice were found. The GDG used the evidence from the literature and their professional opinion to develop recommendations on eliciting patients' information needs. The GDG considered that good communication skills are needed to elicit patients' information needs and there is particular importance in considering how best to overcome barriers to communication such as language difficulties.

4.8.2 Method of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies – we initially included only randomised controlled trials (RCTs) and systematic reviews (SRs) however none of these types of studies were found to meet the criteria. We increased the search to include any type of studies to find relevant information to meet our inclusion criteria.

Types of participants - people prescribed medicines for a medical condition.

Duration of studies – no time limit specified for the studies.

Types of interventions - any intervention (tool) which elicits patients' information needs. The tools had to be brief enough to be utilised within a consultation between the patient and practitioner. Therefore long questionnaires were excluded as they would not be manageable.

Types of outcome measures – any outcome relating to the use of the tool was acceptable as we were looking for a tool which could be utilised within a consultation, rather than looking for specific clinical outcomes.

4.8.3 Evidence review

No tools designed for use in clinical practice were found. The tools in this review were research tools opposed to clinical tools which could be used in a

consultation. We decided to include studies which used these research tools to illustrate some questions that could be asked to the patient in a consultation. Most studies were in questionnaire form and so we included those which were shortest – and so could possibly be used in a consultation. We have not reported the parts of the questionnaire which were not relevant and feasible in a consultation.

One Cochrane review (included in section 5.4) addressed ways of eliciting patients' information needs. **Kinnersley (2007)** [32] conducted a Cochrane review of the effects of interventions before consultations designed to help patients address their information needs. The settings and populations varied but most were conducted in the USA. They stated that it complemented other Cochrane reviews by Wetzels (2007) [34] and Lewin (2001) [30]. The inclusion criteria were RCTs of interventions intended to help the patients, representatives or carers address their information needs in a consultation. This was done by encouraging question-asking, to express their information needs, to overcome barriers to communication and to clarify their understanding of the information provided. Outcome measures were the consultation process, consultation outcomes and service outcomes. 33 trials described in 35 studies met the inclusion criteria. Of the studies assessing single interventions for patients 15 included written materials, four were coaching. The multiple component single interventions studies four had coaching and written materials. Seventeen studies measured question-asking with 6 finding statistically significant increases and 11 studies finding no effects of the interventions compared to controls. Patient participation was measured in 14 studies, it was increased in 8, showed no effect in 5 studies, and in one study it increased initially then decreased. Patient satisfaction was measured in 23 studies, in 14 studies there were no changes and in 5 there was increased satisfaction. Patient knowledge was measured in 5 studies with reduction in two studies and no changes in 3 studies. According to type of intervention, comparisons between written alone and coaching alone showed similar, small to moderate and statistically significant increases for both types for question-asking. Patient satisfaction was borderline statistically significant for written materials, for coaching the effect was small and statistically

significant. Written materials led to a small and statistically significant increase in consultation length, for coaching the increase was smaller but was not statistically significant. Interventions immediately before the consultation led to a small statistically significant increase in consultation length and patient satisfaction.

It should be noted that many of the studies were from other settings: Brown (1999, 2001), Bruera (2003), Butow (1994, 2004), Davison (1997, 2002), Ford (1995), Oliver (2001) were cancer studies. Finney (1990), Kim (2003), Lewis (1991) were from paediatric and family planning settings.

Strydom (2001) [61] conducted a study of a service-user questionnaire to find gaps in medicines knowledge and information sources. This study specifically involved finding out the views of those with learning disabilities. Twenty-one participants were included who were either currently taking prescribed medicines (GP or specialist health services) or had taken in the recent past. Two thirds of the subjects received help with taking their medicines. A questionnaire was designed by the authors using previously published guidelines. They used structured and semi-structured sections, including open questions. The questionnaire was delivered by one of the research team with experience of communicating with people with learning disabilities. The questionnaire was designed to find out their experiences and opinions of using medicines.

A table was given in the paper to show the questions relating to medicines knowledge. Please note that it is unknown as to whether this was exhaustive. The open questions were not reported in the paper.
- Can you read the label? (yes, no)
- What is written on the label? (don't know, name, my name, chemist's name, dose, other)
- What is your medicine called? (don't know, brand or generic name, approximate name, description)

- What are you taking medicine for? (don't know, knew indication, approximate indication)
- Is there anything you should not do while taking this medicine? (don't know, yes, plus example)
- Are there any side-effects? (don't know, one, two or more)

The resulting answers led to the framework for a structure of a patient information leaflet for people with learning disabilities who take medicine for psychiatric conditions. It is not clear as to whether the service users who filled in the questionnaire were taking psychiatric medicine or another type of medicine. The subjects were 'selected for their range of experiences of taking medicines'. Therefore this study does not elicit patients' information needs in total, but how to elicit the knowledge gaps of those with a learning disability.

Duggan (2000) [63] developed and evaluated a survey tool (intrinsic desire for information) to find out patients' perceptions and information needs in regard to their medicines. It was tested for reliability and by factor analysis and was used with 2 cohorts of patients in East London (sample of 500).

Astrom's (2000) [64] paper refined and validated the IDI into a 12-item scale. They included 5 open questions which were a joint construction of the project aims and questions from Lindegren (1999), which was a Masters thesis at the Department of Bio pharmaceutics at Uppsala University. The open questions were transcribed at the bedside of 299 patients in the wards of three medical hospitals in London. Astrom (2000) concluded that the desire for information may be more complicated and involve an emotional or behavioural component, which was not included. It should be noted that this is a desire for information which may differ from information needs.

The 12-item scale was deemed too long to meet our inclusion criteria, however some of the open questions may be of relevance.

The IDI (for reference only):
Part 1 – Demographic details.

Part 2 – Questionnaire items (scored from strongly agree through strongly disagree on a 5-point Likert scale).

1. I always speak to my pharmacist when I want information about my medicines.
2. Sometimes I feel a little inhibited when I ask for information…they might think I should know already.
3. If there is anything I need to know, it's most convenient to ask at the surgery.
4. It's not really my place to ask for information, they have enough to do.
5. The people at the hospital can easily give me information when I go for my appointment.
6. I need as much information about my medicines as possible.
7. Too much knowledge is a bad thing.
8. You can never know enough about these things.
9. I don't need any more knowledge about my medicines/illness.
10. I read about my medicines/illness as much as possible.
11. What you don't know (with respect to medicines/illness) doesn't hurt you.
12. I find information about my medicines/illness confusing.

Open questions:

13. What kind of information about your medicines do you want? Why?
14. How do you want your information to be presented (written, oral, both, other)? Why?
15. Who would you like to give you information about your medicines? Why?

16. When would it be best to have the information about your medicine presented (at hospital, at home, at the community pharmacy, at the GP's)? Why?

17. Would you like to sit down and talk about your medicines with a pharmacist at the hospital?

Zwaenepoel (2005) [65] used the IDI scale and 5 open questions in a survey of the need for information of 279 psychiatric in-patients in Flanders.

Ende (1989) [39] created the Autonomy Preference Index (API) which, as well as a decision-making preference scale had an eight-item information-seeking preference scale. The instrument was in questionnaire format and the scales were developed by a group of 13 clinicians, medical sociologists, and ethicists who were interested in patient autonomy. Items on the scales were tested for reliability and validity. The final API consisted of an 8-item scale on information-seeking scale (ISS) and a 15-item scale on decision-making. The 8-item ISS consisted of the following items for information-seeking preference, with responses on a five-point Likert scale from 'strongly disagree' to 'strongly agree':

1. As you become sicker you should be told more and more about your illness.
2. You should understand completely what is happening inside your body as a result of your illness.
3. Even if the news is bad, you should be well informed.
4. Your doctor should explain the purpose of your laboratory tests.
5. *You should be given information only when you ask for it.
6. It is important for you to know all the side effects of your medicines.
7. Information about your illness is as important to you as treatment.
8. When there is more than one method to treat a problem, you should be told about each one.

* Scoring for this item is reversed and goes from 5 to 1, rather than 1 to 5.

Five further studies used the Autonomy Preference Index to elicit patients information needs (Langewitz, 2006 [40]; Tortolero, 2006 [41]; Neame, 2005 [42]; Braman, 2004 [43]; Schneider, 2007 [45]; Hill, 2006 [46]). All of the studies used the full length (8-item) information-preference scale except for **Langewitz (2006)** [40] who incorporated only one question from the API to target information needs: 'Even when the news is bad the patient must be informed (information)'. Hill (2006) [46] slightly altered the API questions for psychiatric patients to use.

Agard (2004) [62] conducted a qualitative analysis of semi-structured interviews in Gothenburg, Sweden on 40 patients 60 years and over who were receiving treatment after a heart failure diagnosis. The semi-structured qualitative interview had 4 open-ended questions as an interview guide. The questions were:

1. What is your opinion about the medical information that you have been given?

2. What kind of information is lacking?

3. What information have you been given about heart failure?

4. What is your attitude toward receiving prognostic information?

They were also encouraged to speak about the questions and to raise other issues related to them to ensure their major personal concerns really emerged. To avoid respondents feeling ignorant or embarrassed about not being able to adequately answer questions relating to knowledge they were asked first about the information they had been given, rather than asking directly about their knowledge of diagnosis, treatment and prognosis.

Many patients had a limited understanding of their disease but said they were still satisfied with the information they received. Some were indifferent to, accepted, or were unaware of their low level of knowledge.

They concluded that 'to inform the patient adequately, physicians and nurses should determine the patient's level of knowledge and explore why those patients who have a limited understanding do not assimilate or request information. The information they provide should also be adapted to the patient's capacity, wishes and emotional reactions.'

4.9 How can information about medicines be provided for patients in order to enhance SDM in regard to medicines?

Related references	Evidence statements (summary of evidence)
Trevena (2006) [66]	A systematic review of systematic reviews and RCTs found that communicating with patients about evidence does increase their understanding regardless of what tools used. There was a greater effect if information was structured (either written, verbal or video) or interactive, especially if tailored to the individual.
Trevena (2006) [66]	One systematic review of systematic reviews and RCTs found that probabilistic information is best represented as event rates, rather than words, probabilities, or summarised as effect measures such as relative risk reduction. Illustrations, such as cartoons or graphs appear to aid understanding.
Wills (2003) [67]	One systematic review of information formats concluded that decision support/aids can address patient information needs for shared decision-making. They enable patients to better understand treatment options, including probability information.

4.9.1   Evidence to recommendations

Information provided to patients about treatments increases their understanding whatever the format (verbal, written or video) particularly if the information is structured or interactive and especially when tailored to the individual. The GDG considered that health care professionals need to be aware that individuals will vary in the amount and type of information they require and in how they can best access that information. It was the professional opinion of the GDG that undue emphasis is currently placed on use of leaflets and written information and there is inadequate access to pictorial and graphic information. Examples of useful websites were presented to the GDG showing information presented in a variety of ways and the GDG believed it important to widen knowledge and access to such resources. The GDG considered that information should be provided before prescription and dispensing. The GDG were concerned about possible over reliance on PILs which in their professional opinion were not often appropriate for patients and caused concern and problems after medicines had been dispensed. The GDG were aware of pilot work taking place to improve PILS. The evidence review reported in 4.10 also informed recommendations in this area.

4.9.2   Method of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies: Systematic reviews of randomised controlled trials (RCTs) or randomised controlled trials of interventions involving shared decision-making in the clinical context.

Types of participants: people prescribed medicines for a medical condition.

Duration of studies: no time limit specified.

Types of interventions: any interventions involving shared decision-making in a consultation between a health care professional and patient.

Types of outcome measures: patient-centred communication in the consultation; consultation process outcomes: patient involvement, question asking, preparedness; patient care outcomes: satisfaction, knowledge, self-efficacy; type of interventions involved and type of information.

It should be noted that the remit is for conditions with prescribed medicines and this excludes conditions which require chemotherapy or screening. All RCTs are within this remit, however many of the systematic reviews included populations outside the remit, this is noted where applicable.

4.9.3   Evidence review

Trevena (2006) [66] conducted a systematic review of RCTs and review of reviews structured around three aspects of communication with patients about evidence: patients' preferences and actions; research evidence; and the clinical state and circumstances. These were then translated into three main questions:

- What are the most effective communication tools to improve patient understanding of evidence?
- What are the most effective formats to represent probabilistic information to improve patient understanding of evidence?
- What are the most effective strategies to elicit patient preferences/beliefs/values relating to evidence?

The authors excluded studies that did not address their question; were about patient education; were focused on skills and behaviour outcomes without attempting to increase understanding or knowledge; were concerned with counselling as a therapeutic intervention; or were specific to communication regarding clinical trial participation.

Overlap between the trials included in the systematic reviews and those identified independently was verified and duplicated studies were excluded. Ten systematic reviews of RCTs and 30 additional RCTs were retrieved. The review concluded that communicating with patients about evidence does increase their understanding regardless of the tools used. The authors also found that there was a greater effect if information was structured (either written, verbal or video) or interactive (computer, touch screen, question

prompts) and particularly if the information was tailored to the individual. Probabilistic information was found to be best represented as even rates in relevant groups of people, rather than words, probabilities or summarised as effect measures such as relative risk reduction. Written information was reported to be more effective if illustrations and graphs were used.

The authors did however remark that there could be difficulty in generalising from the literature as the trials were conducted in a wide variety of clinical settings using a range of clinical problems and outcomes.

Wills (2003) [67] conducted a systematic review of patient health information provision and use for treatment decision-making. It included research from the past 10 years focusing on testing different formats of information presentation for patient decision-making. The three types of formats looked at were probability presentations, graphic formats and words vs numbers. They found two studies where participants preferred presentation of medicine in terms of relative risk rather than absolute risk format. They found that people place relative risk information into a simplified format of small or large risks and there is a tendency to seriously under or overestimate their personal risks for health outcomes. There is a need to tailor the format of risk communication to the individual's level of numeracy. In routine clinical encounters information should be presented as balanced, in both positive and negative frames. Graphics can improve the understanding of numerical probability information. However some people may dislike some types of displays or misunderstand them. Consistent finding of individual differences in preferences for probability information in words, numbers of both formats implies a need for routine individualised assessments of patient preferences for format. In conclusion, decision support/aids can address patient information needs for shared decision making. They enable patients to better understand treatment options, including probability information.

4.10 What information about medicines should be provided for patients in order to enhance SDM in regards to medicine?

4.10.1 Evidence to recommendations

The GDG considered that the provision of information to patients is to facilitate informed choice about medicines, and achieve a clear picture of the benefits and risks. The information that should be provided to a patient is dependent on what that patient needs to make a decision and therefore a prescriptive list can not be generated. Patient Information Leaflets (PILs) provided with medicines often do not help in providing information about medicines and in any case are only received after the medicine is dispensed. The GDG did consider some broad areas of information that patients might require and used the evidence from expert reviews, in particular those with patient involvement to inform this. They also considered that sources such as the MHRA leaflet might be useful for patients. The GDG therefore made recommendations about the need to tailor the information to the patient and that practitioners should not assume that PILs will provide adequate or appropriate information for individual patients.

4.10.2 Evidence review

The evidence review is a narrative review. The GDG requested review of current national guidance and reports with a particular emphasis on those where patients' views and perspectives were given priority.

4.10.2.1 Summary of 'Always read the leaflet (2005) Report of the Committee on Safety of Medicines Working Group on Patient Information'[1]

The Working Group on Patient Information received advice from patients and experts on the quality of Patient Information Leaflets (PILs) and how to improve them. Patient organisations identified the following with regards to PILs:

- The quality is variable and language is complex with too much jargon.
- The leaflet is often too busy and the print too small.
- Leaflets are too negative and do not mention enough of the benefits
- The PIL should complement discussion with the prescriber, ideally available in the consultation.
- One PIL can not meet everyone's needs so information on patient organisations for further advice could be given.
- Helpline numbers and website addresses for further information should be mentioned.
- Comparative information and information about lifestyle issues can help in decision making.

Expert views regarding PILs:

- Too much use of jargon.
- The use of capital letters was eye-catching but hard to read.
- Inappropriate punctuation can obscure the message.
- Text in boxes may be skipped over.
- Euphemisms are not helpful when referring to serious side effects.
- Messages should be consistent.
- Language should be clear and unambiguous.

Research[2] showed that patients prioritise four key points of information about a medicine – side effects, dos and don'ts, what it does and how to take it – but different people prefer different orders of priority.

The Working Group recommended the following for an improved readability guideline:

Usability – PILs should be clear and understandable to the reader. This incorporates writing style, typeface, design and layout, headings, use of colour, use of symbols and pictograms. The use of templates so that

information is presented consistently would be useful. (See annex 6). PILS should not be too long and complex.

User involvement in PILs – user testing of patient information is recommended. This should be done under controlled conditions and meeting certain stipulations. User testing of content and impact is important. The production of PILs by companies often occurs at the end of the medicine development process, with little thought of involving patients in writing and testing the information. Views should be at all stages of development.

Communicating Risk

It is fundamental when making an informed decision to understand and weigh up the risk and benefits of a treatment. The working group suggested:

- Use of headlines to summarise the most important messages for safety and effectiveness of using the medicine.
- Information on all the side effects is required by law but must be presented logically and include a description of side effects, estimating frequency and advice on necessary actions.
- Inclusion of the potential benefits to provide balance is important.
- Provide information about the harmful effect itself; the probability of it occurring and how to minimise risk and what actions to take if a problem arises.
- Put the most important information first, include information on benefit, use the right words and use numbers to convey risk. Also a supplementary leaflet of risks and benefits in addition to PILs would be useful.

Trust in the information source is also important. Harms and benefits should be side by side and medicine side effects must legally be provided. Care should be taken to give unbiased and clear statistical information.

To increase trust in PILs transparency of data and certainty of risk estimates may be effective. To avoid unnecessary concerns the use of clear information

on a true scale and the nature of such risks are important, such as using analogies and alternative risk scales to show rarity of risk; describe baseline risk and increased risk; provide further information sources on these risks.

Headlines – It is suggested that information could be portrayed in headlines which should include: why the patient should take the product; the maximum dose or duration of treatment; potential side effects/withdrawal reactions; contraindications; important medicine interactions; circumstances in which the medicine should be stopped; what to do if the medicine does not work or where to find further information. Headlines should also include a firm encouragement for the patient to read the rest of the leaflet.

Balance - It is important to be balanced and convey information on benefits as well as risks in order for the information to be credible. The PIL should therefore include the potential benefits of taking the medicine. Research shows that short factual statements on benefits help weigh the risks and benefits. It must also be compatible with the 'summary of product characteristics', and be useful to the patient but not promotional.

Information to give a balanced account would include:

- Why it is important to treat the disease.
- Whether the treatment is for short term or chronic use.
- Whether the medicine is being used to treat the underlying disease or for controlling symptoms.
- Whether the effects will last after medicine stopped.
- Where it is to treat two or more discrete indications, all should be succinctly described as above.
- Where to obtain more information on the condition.

Side effects

Better information about side effects would include:

- Logical order - the most important information should be first e.g. situations where need to take action such as stopping medicines or getting medical help.
- What to do if encounter serious problems.
- Estimates of frequency should be mentioned – as the most serious side effects are also the rarest.
- Use the right wording – not just describe the side effect but convey seriousness/severity.
- Many side effects are dose related and so a warning statement is needed but should not alarm those prescribed high doses.
- It would be useful to have a glossary of lay terms – so there is standardised side effect lay terminology across medicines.

Expression of risk

Expressing statistical risk in PILS:

- Quantifying risk using absolute numbers.
- Verbal descriptors of risk only used if accompanied by equivalent statistical information.
- Convey uncertainty around risk estimates; frequency ranges; duration of risk; frequency estimates based on spontaneous adverse medicine reaction data; constant denominators.

Concepts deemed inappropriate by the Working Group were:

- NNT/NNH.
- positive framing and negative framing – too cumbersome and lengthy.
- use of diagrams – constraints in size.

Supplementary information - a leaflet about risks and benefits in addition to PILs would be able to go into more detail.

Meeting the needs of special groups of patients

Not everyone finds it easy to access and use information in the PIL, e.g. visually impaired people, people whose English is not their first language, people with poor literacy and numeracy, those with learning difficulties or physical difficulties.

Suggestions are made and projects described to help these patient groups:

For health literacy:

- A health search engine for healthcare staff and public.
- Patient information bank for NHS trusts to print consistent information for individuals on their care and treatment.
- Power questions to ask in consultations.

Poor basic skills:

- Clearly written in plain English.
- Signpost other sources of information.
- Helplines.

Patients with sight loss:

- Leaflets in Braille or large print.
- Audio version.
- Leaflets on the web.
- Digital television.
- Telephone helplines and automated voice systems.

Fluency in English difficulties:

- Provision of leaflets in other languages from the company in written or web-based format.

- Telephone helplines.
- The use of translator services.

Medicines for children and young people

- Information for children should be communicated by parents or carers and so leaflets should be aimed at adults.
- Information for young people should take into account their lifestyle of the age group and likely questions.

Provision of information for carers

- Carers may not be in the consultation when prescribed and may need training on administration techniques.
- Outside power of the group but use of a telephone helpline could address some concerns.

The Pharmaceutical Companies

Responsibilities:

- It is suggested that the pharmaceutical industry could promote access to the information on the PILs and other measures.
- Portfolio of Information keys for pharmaceutical companies – use these to help identify additional measures that would promote the dissemination of information on safe use of their products to ensure vulnerable groups can access it.
- Leaflets in other formats; how to signpost these other formats; translation into other languages; use of information mediators such as helplines; expert sources of advice. The PIL can be a pointer to other sources of information for vulnerable groups e.g. booklets, simplified leaflets, magazines and websites.

The information format of the patient leaflet is very important and should be clear and understandable. The information needs to be balanced, trustworthy, and include benefits as well as side effects, with the most important information highlighted. The communication of risk should be conveyed with seriousness but without alarm for the patient. Where to get extra information should be mentioned, if not a separate detailed booklet given. It would be very good practice to have patients test the leaflet to see its appropriateness. Special groups of patients should be taken into account while producing PILs.

Changes to legislation

Since publication of the document 'Always read the label' in 2005, there have been changes made to the European Commission regulations regarding patient information leaflets in response to this report. These included provision of the PIL in formats which are suitable for the blind and partially-sighted; requirement of a specific order for the appearance of the required information on the leaflet; and the requirement of consultation with target patient groups (user testing) to ensure legible, clear and easy to use PILs. These areas were important in the report and it is hoped that they will improve patient information leaflets to support the information provision by health care providers.

4.10.2.2   *Raynor (2007)* [68] *Summary*

Raynor (2007) [68] researched the role and effectiveness of written information available to patients. They conducted a quantitative review of the effectiveness of written medicines information; a qualitative review of the role and value of the information; stakeholder workshops to elicit stakeholder perceptions of the key issues surrounding information presentation to patients; and an information design review.

The workshop discussions found timing of the delivery of the information important, which was often presented after the medicine was prescribed. Sometimes no leaflet was available at all. They found too much information to be overwhelming, harder to understand, often frightening and often too much irrelevant information. Readability was the most important part of written

medicines information – the size of text and content, meaningful information and not jargon.

Other information of importance:

- Dosage and ingredients.
- When and how long to take it.
- The likelihood of it being successful.
- Side-effects e.g. how common or rare they are.
- Factors relevant to their personal medical condition.

Also the role of medicines:

- How to take the drug effectively.
- Its potential side-effects and interactions.
- How to reduce potential harm from medicines.
- How long before the medicine will have beneficial effects.
- Why it is necessary to finish the course.
- Why it was recommended not to drink alcohol.

What makes medicines information effective?

- Timing of delivery of the information – more effective during the consultation.
- Visually appealing and straightforward to read.
- No jargon.
- Basic information about what the medicine contains.
- Designed for patients or professionals.

What participants feel makes medicines information valuable?

- Looks and feels important and highlights priority information.
- Permits an informed choice.
- Is reassuring and reduces concern, conflict and anxiety about whether the medicine is the right one for them.
- Gives them confidence in taking medicines.

4.10.2.3 The 'Medicine use review: Understand your medicine' NHS report[4] summary

The 'Medicine use review: Understand your medicine' NHS report[4] suggests questions patients should ask about their medicines. These could be adapted (as below) into written information for patients:

- What the medicine does.
- Why is it important to take the medicine.
- Other treatment options.
- When and how it should be taken.
- How long it should be taken for.
- What medicines, drinks, foods or activities the patient should be aware of when taking the medicine.
- What the patient should do if they do not feel well when taking it.
- How the patient can tell if it's helping.
- How the patient can be sure it's safe to take it.
- The possible risks and side effects.
- What to do if they get one of the side effects.
- What happens if the patient stops the medicine or takes a lower dose.
- Is there anything they can do to remember to take their medicines.
- Where to go for more information.

4.10.2.4 "Taking Medicines" leaflet summary

The Medicines and Healthcare products Regulatory Agency (MHRA) have produced a leaflet for patients called 'Taking Medicines – some questions and answers about side effects'. The leaflet has 8 questions and short answers to these questions. Patients are advised that they should receive a patient information leaflet with their medicines, and to ask their doctor, pharmacist or NHS direct if they have further queries. The questions in the leaflet are:

1. What do medicines do?
2. Will my medicine cause side-effects?

3. What is meant by a common or rare side effect?

4. How much medicine should I take?

5. How can I reduce the risk of side effects?

6. Do side effects always come on straight away?

7. What should I do if I feel unwell after I take my medicine?

8. Will my medicine affect my lifestyle?

1 Always Read the Leaflet: Report of the Committee on Safety of Medicines Working Group on Patient Information (2005). The Stationery Office, London.

2 Berry, D.C. (1997) Psychol Health. As referenced in Always Read the Leaflet: Report of the Committee on Safety of Medicines Working Group on Patient Information

4 The 'Medicine use review: Understand your medicine' (2005) NHS Report by MHRA and ASK.

4.11   Mental capacity narrative

Some concern was expressed by the GDG about the potential conflicts between respecting the autonomy of the patient and the duty of care felt by practitioners towards the patients. The GDG discussed the importance of professionals' codes of conduct and the legal system in protecting both patients and professionals. The narrative below brings together the principles discussed and is a repeat of section 3.4 in chapter 3.

4.11.1   Roles and responsibilities of patients and health care professionals

Hyperlink to section 3.3 Roles and Responsibilities of Patients and Health Care Professionals

4.12 What information about shared decision-making and adherence should be recorded in patients' notes?

4.12.1 Evidence to recommendations

The GDG considered it important that a record is kept of discussions between health care professionals and patients about medicines. Prescribing and taking of medicines is a long term dynamic process which may involve multiple interactions between health care professionals and patients. Good record keeping aids continuity of care by providing information for healthcare professionals to review the discussion they or other health care professionals have had with patients about their medicines. The GDG made recommendations based on professional opinion.

4.13 What tools are available to support the patient in reaching an informed decision? How effective are these tools?

Related References	Evidence Statements (summary of evidence)
O'Connor (2003) [69]	One systematic review found that there a variety of decision aids used in studies - audio guides, CD-ROMs, web-based, interactive video-disc, lecture and handouts.
O'Connor (2003) [69]	One systematic review found that decision aids led to greater knowledge, realistic expectations, lower decisional conflict from feeling informed, more active in decision-making and less indecision after the intervention.
O'Connor (2003) [69]; Montgomery (2003) [70]; Weymiller (2007) [71]; Thomson (2007) [72]; Oakley (2006) [73]	Decision aids reduced decisional conflict (1 systematic review, 4 RCTs).
Thomson (2007) [72]	One RCT, where decision aids decreased decisional conflict, found that those who used the aid but had not started warfarin treatment were less likely to do so than the control group (who received evidence-based guidelines).
O'Connor (2003) [69];	Decision aids improved patient knowledge (1

Montgomery (2003) [70]; Weymiller (2007) [71]; Thomson (2007) [72]	systematic review, 3 RCTs).
O'Connor (2003) [69]	One systematic review found that simpler decision aids compared to detailed decision aids showed a statistically significant improvement in knowledge, more realistic expectations and greater agreement between values and choices.
Montgomery (2003) [70]	One RCT found that decision analysis decreased decisional conflict more than a video/leaflet intervention.
Fraenkel (2007) [74]	One RCT found that an interactive computer tool which generated personalised feedback statistically significantly improved decisional self-efficacy and preparedness to participate in decision-making, with greatest benefit for older adults.
Oakley (2006) [73]	One RCT found that a workshop plus a decision aid (identifying own risk and pros and cons) and worksheet did not statistically significantly improve adherence, although patients were initially satisfied with the information on medicines this was non-significant and had dissipated by the end of trial.
Hamann (2007) [75]	One RCT found that a decision aid and planned talk with doctor reduced hospitalisation for schizophrenic outpatients. However those who showed a higher preference for autonomy and better knowledge showed a statistically significant higher re-hospitalisation rate.

4.13.1 Evidence to recommendations

The literature review found a number of systematic reviews concerning decision aids and their use. The results of the trials primarily related to decisional conflict, satisfaction, involvement in decision and participation with little effect on health outcomes overall. The GDG considered the evidence supportive of the importance of structured information in a variety of formats to patients but did not feel it appropriate to make specific recommendations regarding decisions aids.

4.13.2 Methods of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies: systematic reviews or randomised controlled trials (RCTs) of tools to help the patient reach a decision (decision aids).

Types of participants: people prescribed medicines for a medical condition faced with a decision.

Duration of studies: no time limit specified.

Types of interventions: any interventions which aid the patient in making an informed decision.

Types of outcome measures: patient outcomes: decisional conflict, patient knowledge, and self-efficacy.

It should be noted that the remit of the guideline is for conditions with prescribed medicine and this excludes conditions which require chemotherapy or screening. All RCTs are within this remit, however many of the systematic reviews included populations outside the remit, this is noted where applicable.

4.13.3 Evidence review

O'Connor (2003) [69] conducted a Cochrane review of decision aids for people facing health treatment or screening. They included RCTs; involving those

over age of 14 making decisions about screening or treatment options for themselves, a child, or significant other; including decision aids and looking at whether the decision aids achieved their objectives. They found 131 decision aids developed within the previous five years, 94 were web-based, 14 paper-based and 12 videos with print resources, eight were audio-guided print resources, two were CD-ROMs and one a web-based with workbook. Most of the decision aids were intended for use before counselling. Decision aids were better in terms of greater knowledge, realistic expectations and lower decisional conflict related to feeling informed. They increased the proportion of people active in decision-making and reduced the proportion of people who remained undecided post-intervention. Simpler decision aids were proven to have more statistically significant improvement than more detailed decision aids in knowledge, more realistic expectations and greater agreement between values and choices. There was no improvement compared to comparisons for affecting satisfaction with decision making, anxiety, and health outcomes.

Only a few of the studies in this systematic review were relevant to the guideline as the majority of studies included were surgery, screening, or other populations not included in the medicines concordance remit. The studies that were relative to the guideline were seven trials of hormone replacement therapy* (audio guides, booklet and interactive videodisc, mix of lecture and handouts); two trials involving Ischaemic heart disease**, interactive videodisc and a videocassette; and one study of atrial fibrillation treatment*** (audio guide deciding whether to change from aspirin to warfarin). All studies except five of the HRT trials compared a decision aid with usual care. The other five studies compared a multiple element design with a simple decision aid.

*McBride 2002, Murray HRT 2001, O'Connor, 1998-RCT, Dodin 2001, O'Connor Wells 1999, Rothert 1997, Rostrom 2002.**Morgan 1997, Bernstein 1998.***Man-Son-Hing 1999.

Montgomery (2003) [70] conducted a factorial randomised control trial to evaluate two interventions to help hypertensive patients decide whether to start medicines to reduce blood pressure. This was carried out in 21 general

practices in SW England with 217 patients aged 32 to 80 years (mean age 59 years), who were newly diagnosed with hypertension. Patients were allocated to decision analysis or no decision analysis, they were then further randomised to video/leaflet or no video/leaflet groups. The decision analysis in this case was a decision tree for hypertension which used a computerised self-completed interview to assess patients' utilities with minimal input from researcher and the absolute cardiovascular risk was calculated. The video was informational about high blood pressure. The information booklet included four fact sheets from the British Hypertension Society. The primary outcome was the total score on the decisional conflict scale, a questionnaire measuring how uncertain about the course of action to take and factors which could be changed that lead to the uncertainty. Secondary outcomes were subscales of the Decisional Conflict Scale and intentions about starting treatment, state anxiety, knowledge of hypertension, actual treatment decision.

Both interventions successfully reduced patients' total decisional conflict at follow-up. Decision analysis decreased the decisional conflict more than the video/leaflet. Total decisional conflict mean for decision analysis was 27.6 (s.d=12.1), no decision analysis 38.9 (s.d=18.3) adjusted difference -9.4 (95% CI -13.0 to -5.8) p<0.001; video/leaflet 30.3 (s.d=13.4) and no video/leaflet was 36.8 (s.d=18.8), -4.2 (95% CI -7.8 to -0.6), p=0.021. The Decisional conflict subscales showed a clear reduction in three of the five subscales - uninformed 23.7 (s.d=11.8) compared to no decision analysis 40.7 (s.d=23.1) adjusted difference -15.7 (95% CI -20.2 to -11.2), unclear values 28.4 (s.d=14.7) vs 43.8 (s.d=24.3) adjusted difference -13.1 (95% CI -18.0 to -8.1) and unsupported 24.4 (95% CI 13.4 vs 34.8 (18.3) adjusted difference -8.7 (95% CI-12.8 to -4.7) and some evidence for reduction in uncertainty and no evidence for decision quality. The video/leaflet intervention showed no evidence in these last two subscales and there was only clear evidence on the uninformed subscale. For the intention to start treatment when followed up the adjusted risk ration: yes versus unsure 1.19 (95% CI 0.59 to 2.40) for decision analysis and 1.80 (95% CI 0.89 to 3.63) for the video/leaflet. No versus unsure 3.15 (95% CI 0.91 to 10.98) and 0.52 (95% CI 0.15 to 1.77) respectively. The overall p values were 0.09 and 0.17 respectively. Actual

prescription of medicine was not different for either intervention or controls. There was a suggestion (p=0.055) that anxiety may be reduced by decision analysis although the evidence there was weak and no evidence of this for the video/leaflet intervention. Both interventions statistically significantly increased knowledge of hypertension. Those who received both interventions had the lowest decisional conflict (27.1 compared with 28.2 and 33.3 and 44.2 for decision analysis only, video/leaflet and control). They had a high knowledge score – the same as video/leaflet. Within the regression models there was a statistically significant (antagonistic) interaction between decision analysis and video/leaflet, so the effect of each was reduced by the presence of the other (interaction coefficient 12.5, 95% CI 5.4 to 19.5, p=0.001 for decisional conflict and -9.1, 95% CI -16.3 to -1.9, p=0.013 for knowledge. This study was followed up in 2005 by Emmett, who found that there was no evidence of any difference in blood pressure, cardiovascular disease risk for either intervention or between them. There were also no effects on medicine prescribing, self-reported adherence, consulting behaviour or management changes.

Weymiller (2007) [71] conducted an RCT study of the effect of a decision aid on statin medicine decision-making. The study was conducted in a diabetes referral clinic in Minnesota, USA. Ninety-eight participants were included with a mean age of 64 (s.d=12) for the decision aid group and 66 (s.d=8) for the control group. Participants were randomised to either receive usual care plus a standard pamphlet on cholesterol management or a statin choice decision aid. The decision aid included name, cardiovascular risk factors, an estimated level of cardiovascular risk (3 levels) and the absolute risk reduction with statins and the potential disadvantages of taking them. A question prompted patients to express whether they were ready to make a decision and if they wanted to take statins, discuss the issues with their clinician or other. After the consultation the participants were given a questionnaire to complete. The outcomes of interest were improvement in patient knowledge and reduction in decisional conflict. Seventy-four% would recommend the decision aid to others compared to 53% of control patients recommending the pamphlet, (OR 2.6, 95% CI 0.8 to 8.0), 68% would want to receive similar support for future decisions compared to 58% of control patients (OR 1.5, 95% CI 0.6 to 3.8).

Those receiving the decision aid had higher knowledge scores than the control group and those allocated to receive the intervention during the visit achieved better knowledge than those who received before the consultation. The intervention group had statistically significantly less decisional conflict afterwards than the control group, and at 3 months (although not statistically significant). Those in the DA group felt more informed. Thirty percent of the DA group (6/7 were from the DA during the visit group) decided to start statin therapy immediately after, compared to 21% of the control group. At 3 months 63% of the DA group and 63% of the control group reported taking statins (OR, 1.4, 95% CI, 0.8 to 2.4). Overall, there was no difference in adherence to patient choice at 3 months.

Thomson (2007) [72] conducted a randomised controlled trial of a decision aid for anti-thrombotic treatment of patients with atrial fibrillation. One hundred and nine patients aged over 60 years from 40 general practices in the Northeast of England. The intervention involved the doctors in the clinic delivering either the decision aid or guidelines to the patient. The decision aid was a computerised aid which presented the individualised benefits and potential harms of warfarin treatment and participants were invited to weigh up the advantages and disadvantages of treatment before coming to a shared decision with the doctor. This involved personalised risk assessment using the Framingham equation for stroke risk and the presentation used graphical and numerical formats followed by a shared decision-making component. The evidence-based guidelines group applied decision analysis derived guidelines according to the participants' risk factor profile and the recommendation made directly to the participant by the clinic doctor. The primary outcome measure was decisional conflict immediately after the consultation. Secondary outcomes were anxiety, knowledge and decision-making preferences. The computerised decision aid group had lower decision conflict immediately after the clinic (mean -0.18, 95% CI -0.34 to -0.01) and mean -0.15 (95% CI -0.37 to 0.06) at three month follow-up. Both groups had less decision conflict after the consultation but the difference between groups was statistically significant at 5% level. Subscales suggested this was due to feeling more informed and clearer of their personal values for the risks and benefits of alternative options.

The reduction in anxiety fell statistically significantly but was not different between groups. Knowledge scores improved slightly after the consultation but at three months were back at baseline level. Participants in the decision aid group were less likely to start warfarin than those in the guideline arm (39/53, 73.6%) compared to guidelines (50/56, 81.7%), RR 0.82, 95% CI 0.68 to 0.99. This was mainly caused by the group who were not already on warfarin. The differences in starting warfarin for this group was 4/16 (25%) in the decision aid group, compared to the guideline group15/16 (93.8%), RR 0.27, 95% CI 0.11 to 0.63. There was no difference in health outcomes 3 months after the clinic.

Fraenkel (2007) [74] conducted a randomised control trial which tested the efficacy of a computer tool to improve informed decision-making for patients with knee pain in an outpatient clinic. The trial was conducted in a primary care outpatient clinic in the USA. Eighty-seven participants over the age of 60 were randomised to receive an Arthritis Foundation information pamphlet (control group) or to perform an Adaptive Conjoint Analysis (ACA) (intervention group). The ACA is an interactive computer tool which could generate immediate feedback to the participant and help them construct treatment preferences by means of trade-offs by rating tasks. The treatment characteristics in the ACA task included route of administration, likelihood of expected benefit, and risk of adverse effects. Questionnaires were given to assess outcomes. Decisional self-efficacy and preparedness to participate in decision-making remained statistically significantly higher in the intervention group than the control group after controlling for race and health status. Arthritis self-efficacy was of borderline significance. Outcomes by age and education suggest older adults may be the most likely to benefit. Ninety eight percent of the participants thought the ACA task was very easy/easy to do. The patients in the intervention group had greater self-confidence in their ability, felt more prepared to participate in shared decision-making and felt they had greater self-efficacy over arthritis than the control group.

Oakley (2006) [73] assessed the effectiveness of a decision aid on patient adherence to oral biphosphonate medicine. They conducted an RCT with

postmenopausal women over the age of 65 who were diagnosed with osteoporosis. Thirty-three participants were included in the study, with a mean age of 77 years (range 61-90). The intervention group attended an osteoporosis workshop, where they were given a decision aid and group discussion on a worksheet. This included working through the decision-making process and identifying their own lifetime risk of hip fracture, personal and family health issues which may influence their decision, and self-care options already using or willing to try. They were to consider the pros and cons and their personal values regarding therapy and noted any questions for the GP on a worksheet. Two weeks later they returned with their worksheets for a follow up with a GP osteoporosis specialist. Questionnaires were then administered to establish compliance. The difference in adherence improvement was not statistically significant. Satisfaction with information about medicines improved initially in the intervention group but by the final questionnaire this effect had dissipated to non-significance. The decisional conflict scale showed a reduction in decisional conflict from baseline measures (total DCS score pre-intervention, median 2.5 (1.8-3.4) v 2.0 (1.0-2.4) post-intervention, p<0.001, however this cannot be compared to the control group as they were not assessed for this measure. The decision aid improved their ability to make a decision about which treatment was best and to discuss their medicine with the GP. However it had no obvious effect on adherence.

Hamann (2007) [75] conducted an RCT to assess whether shared decision-making in antipsychotic medicine choice would influence long-term outcome. 86 patients with a diagnosis of schizophrenia were included and followed up, 58% female with mean age of 38 years (s.d=11.4), mean duration of illness 9.2 years (s.d=8.5). The study was conducted in Germany. The intervention group received a decision aid program and the control group received usual care. The decision aid was a 16 page booklet with the pros and cons of oral versus depot formulation, first versus second generation antipsychotics, psycho-education and a type of socio-therapeutic intervention. Twenty-four hours after working through the booklet with the trained nurses the patients consulted with the psychiatrists on further treatment. The patients then filled

out questionnaires relating to patient involvement, satisfaction and psychopathology. Patients were followed up at 6 and 18 months after discharge from hospital. Univariate analysis found no statistically significant differences between groups. When multivariate analysis was conducted to control for the re-hospitalisation rate it showed that there was a positive trend for the decision aid and planned talk in reducing rehospitalisation. Higher participation preferences (OR=1.06, p=0.03) and better knowledge (OR=1.23, p=0.03) rates statistically significantly predicted rehospitalisation. No other effects were shown.

4.14 How can a practitioner elicit whether a patient agrees with the prescription recommended by the practitioner?

Related references	Evidence statements (summary of evidence)
	No evidence was found on specific clinical tools that can aid the practitioner in eliciting whether patient agrees with the recommended prescription.

4.14.1 Evidence to recommendations

No tools designed for use in clinical practice were found. The GDG used the information from the research studies and their professional opinion to make recommendations in relation to elicitation of agreement with decision to prescribe.

4.14.2 Methods of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies – no restrictions on study design.

Types of participants - people prescribed medicine for a medical condition.

Duration of studies - no time limit specified.

Types of interventions - any interventions intended to assess tools that can aid a practitioner in eliciting whether a patient agrees with recommended prescription.

Types of outcome measures – agreement with prescription, patient satisfaction with issued prescription.

4.14.3 Evidence review

No study was found that assessed a clinical tool that could aid a practitioner in eliciting whether a patient agrees with the recommended prescription. One prospective observational study (Bikowski 2001) [76] that aimed to characterise the degree of disparity between physicians' perceptions of older patients' medicine regime and patients' perceptions of their regime within a community family medicine residency setting.

Eligible patients were aged 65 years and older, non-institutionalised, visiting the clinic on the index day for a routine visit, had seen the index physician at least three times in the past calendar year, and, by brief review of the medicine flow sheet, were taking at least four prescriptions medicines. The study sample comprised 50 physician-patient pairs.

Physicians were given the patient's chart, with a request to complete a questionnaire that asked for information on all prescriptions and non-prescription medicines, with dosages and frequencies of administration. Patients were interviewed at home by first year medical students who received specific training for the study.

Percentage congruence - defined as agreement between physician and patient regarding all prescriptions medicines, dosages and frequency, was calculated for each pair. Complete congruence was showed for 14% of the 50 physician-patient pairs; 74% had at least one medicine that either the physician was unaware the patient was taking or the physician thought the patients was taking but that was not part of the patients regime; 12% had dose and/or frequency differences, however they agreed upon the medicines in the regime.

Antihypertensive medicines were the most commonly prescribed medicine, accounting for 36% of the total. The highest congruence was found for diabetic and other endocrine medicines. Pain medicines and gastrointestinal medicines showed the lowest congruence.

4.15 What aspects of consultation style increase patient involvement in decision-making?

Related References	Evidence Statements (summary of evidence)
McKinstry (2006) [77]	One high quality systematic review found that there is insufficient evidence to conclude that any intervention may increase or decrease trust in physicians.
van Dam (2003) [78]	One systematic review of RCTs found that supporting patient participation in diabetes care and self-care behaviour (i.e. by assistant-guided patient preparation for visits to doctors, empowering group education, group consultations, or automated telephone management) is more effective than changing provider consultation style for improving patient self-care and diabetes outcomes.
Edwards (2004) [79]	One RCT reported statistically significant effects of the research clinic group (which provided more consultation time) in confidence in decision and expectation to adhere to chosen treatments.
Cohen (2004) [80]; Edwards (2004) [79]	Two studies from the same randomised controlled trial found that training GPs in SDM or combined with risk communication yielded conflicting results in the probability of a prescription being issued to patients.

Cohen (2004) [80]; Edwards (2004) [79]	Two studies from the same randomised controlled trial found that training GPs in SDM or combined with risk communication yielded no effect on the probability of investigations, referrals or follow-up GP visits for any of the conditions.
Savage (1990) [81]	One RCT found that a directing style of consultation yielded statistically significantly higher levels of satisfaction on almost all the outcome measures compared to a sharing style. This was particularly relevant for patients with physical problems.
Shields (2005) [82]	One RCT reported a statistically significant likelihood of a physician promoting collaboration in treatment decision-making and exploring issues around the disease and illness with patients rather than with companions of the patients e.g. physicians were more likely to be responsive to being patient-centred when the patient raised the issue than when their companion raised it. There was no difference in level of patient-centeredness between the unaccompanied and accompanied visits.
Shields (2005) [82]	One RCT reported a statistically significant responsiveness of a physician to explore the disease and illness when the issues were raised by the patient compared with the companion of the patient.

4.15.1 Evidence to recommendations

The GDG were aware that there is anecdotal evidence that practitioners and patients report that the quality of the practitioner-patient relationship is important in decision–making. The quality of the practitioner-patient relationship was reported as being important in some studies of patients' medicine-taking behaviour as outlined in chapter 3. The quality of a practitioner–patient relationship is likely to be influenced by a number of factors that relate to previous consultations and problems under discussion. The consultation skill of an individual practitioner is also likely to be important regardless of length of professional-patient relationship. It was considered that the level of trust between practitioner and patient may be a key factor in this relationship and the GDG wished to review whether this could be specifically increased in practitioner-patient encounters. The evidence from a recent systematic review suggested that there is insufficient evidence to recommend any specific intervention. The GDG felt that consultation style should be tailored to individual patients to allow full communication.

4.15.2 Methods of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies: systematic reviews or randomised controlled trials (RCTs) that focus on aspects of consultation style that may increase patient involvement in decision-making.

Types of participants: people prescribed medicines for a medical condition faced with a decision.

Duration of studies: no time limit specified.

Types of interventions: any interventions which assess which aspects of the consultation style may increase patient involvement in decision-making.

Types of outcome measures: Patient-centred communication in the consultation; consultation process outcomes: patient involvement, question

asking, preparedness; patient care outcomes: satisfaction, knowledge, self-efficacy, type of information.

It should be noted that the remit is for conditions with prescribed medicine and this excludes conditions which require chemotherapy or screening. All RCTs are within this remit, however many of the systematic reviews included populations outside the remit, this is noted where applicable.

4.15.3 Evidence review

Our searches retrieved two systematic review and 4 RCTs that were considered relevant to the key clinical question.   All the studies looked at the patient-provider interaction, either by exploring the impact of different provider styles or by focusing on patient behaviour changes.

McKinstry (2006) [77] conducted a Cochrane review of interventions to improve the trust of patients in their doctors. They searched 10 databases including the Cochrane Central Register of Controlled Trials, Medline and Embase. The inclusion criterion for studies was RCTs, CCTS, controlled before and after studies and interrupted time series studies. The interventions were any that influenced patients trust in their doctors, or where trust was an outcome of an intervention. The participants were doctors, adults or children using healthcare or those related to them. Outcome measures were an increase or decrease in patients' trust and the components of trust; other healthcare behaviours; health status and well-being; use of resources; satisfaction with care; perception of doctors' communication skills; perception of doctors' humanistic attributes; perception regarding patients' trust; perceptions of doctors trustworthiness. Studies were excluded if they did not measure change in trust or were not the right type of study. Two authors independently assessed whether the titles and abstracts were relevant and four authors assessed the retrieved articles for inclusion. Two authors assessed the quality of each study according to EPOC criteria. A multi-disciplinary advisory group was set up to assess whether there was anything that had been left out of the review. 2099 titles and abstracts were found, five met all the criteria, but two of these referred to the same study and one had insufficient data points before and

after the intervention, therefore leaving three studies. Two of the studies had a primary aim of assessing the impact of the intervention on patient trust. Thom (1999) coached doctors in behaviours known to be associated with trust and Hall (2002) looked at the impact of disclosing financial incentives physicians received for compliance with managed health care protocols on the trust patients had in physicians. In the third study (Thompson 2001), trust was a secondary outcome and compared the impact of three different types of induction visit for new patients of an HMO to those who received no intervention. The trust was in any health care professional. The review detailed the quality of studies including allocation concealment, blinding and protection from contamination. On assessment of study quality all three RCTs provided baseline measures and within and between group differences for measures. Thom (1999) used computer allocation to groups but it was not clear if the researcher was blind to this allocation. The interviewer was blind to the status of the physician but it was unclear if the patients were blinded. Hall (2002) conducted a stratified random sample study and used a computer for allocation with no input from researchers. The interviewers were blind to the patients' status but the patients were aware of their own status. Thompson (2001) did not report how the randomisation was applied. Patients were aware of their status but it is not clear if interviewers were blind to the status of the interviewees. The study by Thom (1999) showed no effect on trust (74.4 for the intervention and 76.2 for the control group, statistically non-significant). Satisfaction or humaneness scores were also statistically non-significant. Hall found a small increase in trust for both groups from baseline and when adjusted this was a 1.4% increase in physician trust ($p < 0.05$). Thompson (2001) found the trust in the health plan health professionals rose statistically significantly following the enrolment visit with health personnel compared to control group $p < 0.001$). The author concluded that there is insufficient evidence to conclude that any intervention may increase or decrease trust in physicians.

Van Dam (2003) [78] developed a systematic review of RCTs that looked at the effects of interventions on provider-patient interaction on patient diabetes

health behaviour, patient self-care, delivered diabetes care and health outcomes, and to disentangle those that are the most effective. Eight studies were included after a rigorous methodological quality assessment, and these showed different interventions on different levels of the provider-patient interaction in diabetes care. Four studies focused on provided consulting behaviour modifications (studies 1-4), and four studies focused directly on patient behaviour change (studies 5-8). All studies were conducted in practical diabetes care, three in hospital outpatient clinics and five in general practices.

The main findings suggest that the most effective interventions are those with a direct approach to support patient participation (i.e. by assistant-guided patient preparation for visits to doctors, empowering group education, group consultations, or automated telephone management) in diabetes care and self-care behaviour, while interventions which focus on change of provider behaviour were less effective. Thus, the authors advocate a shift from the traditional medical model to a more patient-centred, patient participation and empowerment paradigm of delivery of diabetes care. The authors pointed out that the review did present some limitations, illustrated by the small number of reviewed papers; the differences between the studies; and the focus on RCTs.

Cohen (2004) [80] and **Edwards (2004)** [79] conducted a cluster randomised crossover trial with the aim to explore the costs of training GPs in developing SDM competences and in the use of risk communication (RC) aids and to evaluate the effects of such training on a range of service resource variables. Edwards (2004) published the main trial results that focused on the doctor patient interaction, patient outcomes and satisfaction with the decision. Within each cluster, patients were also allocated randomly to consult with the doctor at one of three points in the study. The study comprised three phases. Phase 1 was pre-training. Phase 2 included training for half of the GPs and the other half in RC. In phase 3, each GP received training in the other element making them fully trained in both. The authors argued that in this way, the design offered the greatest potential to gain understanding about the effects of each form of training alone and in combination and if the sequence

of skill acquisition was important. A further randomisation allocated patients to attend either in usual surgery time or in a research clinic- audio taped, including fewer interruptions and more time for each consultation (up to 15 minutes each).

SDM training involved GPs attending two workshops where standardised and previously piloted skill development processes were used. SDM competences were described and demonstrated by means of consultation simulation and pre-prepared scenarios involving the four study conditions. RC also involved attendance at 2 workshops, and the aids consisted of tabulated data and visuals displays of risk estimates for the four study conditions. Patients with one of four conditions (menorrhagia, atrial fibrillation, menopausal symptoms or prostatism) were invited by their GP to attend a "review consultation" to discuss their continuing treatment. Twenty GPs from 20 different practices in South Wales were recruited. Costs of training for both RC and SDM included time of trainers, of those being trained and of the simulated patients used as part of the training exercise. Information on prescriptions, investigations and referrals was obtained from questionnaires completed by each clinician at the review consultation.

Main results published by Cohen (2004) indicated that Training in SDM or combined with RC statistically significantly affected the probability of a prescription being an issue to women with menopausal symptoms and menorrhagia (despite RC alone not having any effect). However, there was no statistically significant change in prescribing for patients with prostatism or atrial fibrillation. There was also no effect on the probability of investigations, referrals or follow-up GP visits for any of the conditions. Training cost was £1218 per GP, resulting in an increase of cost of consultation by £2.89.

Edwards (2004) reported statistically significant effects of the research clinic (which provided more time) in confidence in decision ($p<0.01$) and expectation to adhere to chosen treatments ($p<0.05$). Anxiety scores approached statistical significance for the RC intervention, as did expectation to adhere to the chosen treatment for both interventions. No statistically significant effects of the risk communication or SDM interventions were seen on the whole range of patient-based outcomes.

Cohen (2004) concluded that due to the explanatory nature of the study, no assessment could be made on how training could affect the length of a consultation.

Savage (1990) [81] sought to compare the effects of a directing and sharing style of consultation by a GP on patient's satisfaction with the consultation in a deprived inner city area. Patients were aged 16 to 75 years of age and were randomised to receive a directing or sharing style in the part of the consultation regarding treatment, advice and prognosis. Three hundred and fifty nine patients were randomised, however 120 patients failed to complete the assessment that took place a week later.

There were no statistically significant differences in the mean length of consultations between the two experimental groups. Patients who had the directing style of consultation reported statistically significantly higher levels of satisfaction on almost all the outcome measures, and was particularly strong for patients with physical problems (excellent explanation $p<0.02$; excellent understanding $p=0.04$). There was no statistically significant difference in the responses to the directing and sharing styles in longer consultations, where the main treatment was advice and among patients with psychological or chronic problems. Statistical significance values were not reported. This study was conducted in England.

Shields (2005) [82] evaluated the influence of accompanied visits on physician-patient communication, particularly on patient-centred communication. Thirty patients were included in the study. The participants were aged above 65 years, were not cognitively impaired and had a companion who could accompany them to their next visit. Companions were not assigned a specific role during the session and physicians were not asked to conduct the sessions in any particular way.

There were no statistically significant differences between accompanied and unaccompanied visits for the number of issues raised by patients. However patients did raise more issues in unaccompanied visits. No statistically significant differences were observed for levels of patient-centeredness, or

satisfaction, even if patients who were accompanied reported being slightly more satisfied.

Physicians were more likely to promote collaboration in treatment decision making with patients than with companions ($p<0.0001$). Physicians were also more responsive to issues regarding exploring the disease and illness when the issues were raised by the patient compared with the companion ($p<0.03$). There was no difference in level of patient-centeredness between the unaccompanied and accompanied visits.

4.16 Do interventions to increase patient involvement increase length of the consultation?

Related References	Evidence Statements (summary of evidence)
Evidence from the UK	
McCann (1996) [83]; Middleton (2006) [84]	Two RCTs from the UK found that interventions to increase participation in the consultation (leaflet and agenda form) statistically significantly increased consultation length. The intervention group in the McCann study increased consultation length by 72 seconds (p=0.02). The agenda form group in the Middleton study increased consultation length by 54 seconds, p<0.004. The consultation length increased by 114 seconds for the combined group (education and agenda form (p<0.001).
Little (2004) [36] McLean (2004) [85]	Two RCTs from the UK found interventions to increase participation in the consultation (a prompt to elicit patient concerns and a leaflet) did not statistically significantly increase consultation length.
Middleton (2006) [84]	In one RCT that reported a statistically significant increase in consultation length, the increase was more pronounced when using an agenda form than when using the agenda form in combination with an educational intervention. When using the educational intervention alone no difference was found.
Little (2004) [36]	One RCT reported that the use of a general leaflet

	in the consultation was statistically significantly more effective in increasing satisfaction when consultations were shorter.
Edwards (2004) [79]	Adherence was increased in clinics where more time was available than usual surgery times.
Evidence including the rest of the world	
Kinnersley (2007) [32]; Harrington (2004) [31]; Cegala (2001) in Wetzels review (2007) [34]; Loh (2007) [33]; Hamann (2006) [86]	Evidence from two systematic reviews and three RCTs suggest that interventions designed to improve patient participation in consultations do not increase overall length of consultations. One review (Kinnersley 2007) found 14 RCTs with no statistically significant increase in consultation length and 3 RCTs with a statistically significant increase (Hornberger 1997; McCann 1996 and Middleton 2006 – 2 UK studies reported earlier).
Hornberger (1997) in Kinnersley (2007) [32]	In one of the RCTs that reported a statistically significant increase in consultation length, this increase was due to time spent discussing diagnoses and physical examination.
Kinnersley (2007) [32]	Written materials had a small and statistically significant increase in consultation length compared to coaching where the small increase was not statistically significant.*
Kinnersley (2007) [32]	Interventions immediately before the intervention led to a small and statistically significant increase in consultation length. Whereas those some time before had no effect. **

Kinnersley (2007) [32]	There was no difference in the effect on consultation length (Kinnersley review) in RCTs whether they had additional clinician training or not.***
Hornberger in Kinnersley (2007) [32]	One RCT (from Kinnersley review) reported that overall quality of care showed a statistically significant effect on the intervention group which had a longer consultation time than the control group.

*This result is from a comparison of written materials and coaching for the consultation length of all studies which included written materials or coaching (thirteen), three of which were not relevant to the population of interest in this evidence review.

**This result is from a comparison of studies some time before consultation (2) and immediately before consultation (11), of which three of the immediately before consultation were not the relevant population.

***This result included studies of Clinician training (2) compared to 12 studies where Clinicians were not trained. One of the Clinician training studies and three of the Clinicians not trained studies were not the relevant population

4.16.1 Evidence to recommendations

The GDG were concerned that interventions to increase patient involvement in the consultation might result in longer consultations and have impact resource implication and impact on service delivery more generally. The evidence was mixed. The studies included different health-care settings and different specialities and decisions. The GDG were primarily interested in simple interventions and the evidence indicated that simple interventions might result in increase in consultation length but this did not always occur. The interventions in the studies were however more complex than the recommendations the GDG were making which primarily centre on how practitioners consult. The GDG considered it important to reassure clinicians that increasing patient involvement may not affect consultation length.

4.16.2 Methods of the evidence review

The aim of the literature review is to identify the most relevant, published evidence to answer the key clinical questions generated by the GDG. Due to time constraints, exhaustive systematic reviews (see the Methods of the Cochrane review) were not undertaken. However, the evidence reviews were undertaken using systematic, transparent approaches following the Guidelines Manual 2007 (www.nice.org.uk).

The titles and abstracts of records retrieved by the searches, suggested by the GDG or submitted by stakeholders were scanned for relevance to the key questions. Any potentially relevant publications were obtained in full text. These were then reviewed to identify the most appropriate evidence to help answer the key questions and to ensure that the recommendations are based on the best available evidence. This process required four main tasks: selection of relevant studies; assessment of study quality; synthesis of the results; and grading of the evidence.

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies: systematic reviews or randomised controlled trials (RCTs) that assess whether interventions to increase patient involvement increase length in consultation.

Types of participants: people prescribed medicine for a medical condition faced with a decision.

Duration of studies: no time limit specified.

Types of interventions: any interventions which aim to increase patient involvement and include details of consultation length.

Types of outcome measures: Patient-centred communication in the consultation; Consultation process outcomes: patient involvement, question asking, preparedness; Patient care outcomes: satisfaction, knowledge, self-efficacy in relation to consultation length.

It should be noted that the remit is for conditions with prescribed medicine and this excludes conditions which require chemotherapy or screening. All RCTs are within this remit, however many of the systematic reviews included populations outside the remit, this is noted where applicable

4.16.3 Evidence review

This review was stratified to firstly present the RCTs research from the UK and secondly present systematic reviews and RCTs which include research from other areas of the world.

4.16.3.1   RCTS from the UK

Little (2004) [36] conducted a randomised controlled trial in the UK to assess the effect of leaflets in empowering patients in primary care consultations. Participants were randomised to four conditions: receipt of a general leaflet, depression leaflet, both leaflets and no leaflets (control group). The general leaflet asked patients to list issues they wanted to raise and explained that the doctor wanted them to ask questions, talk and discuss any problems of

concern to them. The depression leaflet listed symptoms of depression (without labelling as such), alerted patients to whether they had these symptoms and that the doctor would like to discuss them. The only statistically significant result was the increase in satisfaction for those who received the general leaflet, the mean difference was 0.17 (95% CI 0.01 to 0.32, p=0.04). The general leaflet was statistically significantly more effective when consultations were shorter (leaflet 0.64, 95% CI 0.19 to 1.08; time 0.31, 0.0 to 0.06; interaction between both showed that consultations of 5, 8, and 10 minute increased satisfaction by 14%, 10% and 7%). The leaflet overall caused a small statistically non-significant increase in consultation time.

Middleton (2006) [84] conducted a randomised controlled trial in the UK of agenda forms completed by the patient and doctors' education about the agenda on the outcome of the consultation. The intervention group were asked to think of a list of their concerns, arrive five minutes earlier and bring spectacles and an interpreter if those were required. The intervention doctors were given a one day educational workshop to allow the doctors to have awareness of the patient agenda model of the consultation. The model involved identifying the agenda (ideas, concerns, expectations and reasoning). The doctors reflected on their own agenda and negotiation of action with patients. Half of the patients in this group filled in an agenda form in the preceding time before their consultation, half did not. The control group included GPs not given the educational programme, and this group was split into half the patients using the agenda form and half not using it. The consultation length for the control group was 7.1 minutes (95% CI 6.5 to 7.7 minutes). The agenda form statistically significantly increased the duration of consultation by 0.9 minutes (95% CI 0.3 to 1.5, p=0.004) and the combined intervention by 1.9 minutes (95% CI 1.0 to 2.8, p<0.001). The educational intervention on its own did not statistically significantly change the length of consultation (0.7 minutes, 95% CI -0.2 to 1.6 minutes). There was a statistically significant increase in both interventions for number of problems identified. The only change in patient satisfaction was increase in depth of doctor-patient relationship from the agenda form group.

McCann's (1996) [83] randomised controlled trial in the UK was of a brief written intervention leaflet 'Speak for Yourself' to increase participation in the consultation read before the consultation compared to those given a control leaflet. The first part asked patients to identify the nature of their problems and to consider their ideas to causes, treatment and effects of the problems. They had space to write down ideas. The second part of the leaflet advises to state their ideas and concerns about the illness to the doctor and ask questions. The intervention group had statistically significantly longer consultations (8.43 minutes, s.d=2.97 versus 7.22 minutes, s.d=2.42, 95% CI -0.44 (0.08, 0.81) and they asked more questions than controls.

McLean (2004) [85] conducted an open randomised controlled trial to see whether a prompt to elicit patients' concerns for minor illness would be beneficial and the costs of doing so. One hundred and ten patients from four training semi-rural general practices in the South-East of the UK took part in the study. The written prompts were 'May I ask if you have any concerns about this "…." (illness/pain) you have come about today?' followed by: 'Anything in particular about the "…"?' and, if still unforthcoming: 'What is it about the "…" that concerns you?' A consultation satisfaction questionnaire regarding the professional care component was given. The doctor had to record the consultation length (estimated to the nearest minute using a clock to note start and end of consultation) and the diagnosis made. The control group received the consultation as normal. The doctor depending on whether the top sheet of a randomly arranged pile of papers said 'control' or 'intervention'. [However it must be noted that the same doctor was conducting both control and intervention and the control condition may inadvertently receive a more patient-oriented consultation]. Patient satisfaction was 80.9 for controls and 88.2 for intervention patients (s.d=11.8), mean difference 7.2 (95% CI 2.0 to 12.6). The consultation length of intervention consultations was on average 1 minute longer for intervention group than controls (11.0 vs. 10.0 minutes), but this was not statistically significant.

Cohen (2004) [80] and **Edwards (2004)** [79] conducted a cluster randomised crossover trial in the UK with the aim to explore the costs of training GPs in developing SDM competences and in the use of risk communication (RC) aids and to evaluate the effects of such training on a range of service resource variables. Edwards (2004) published the main trial results that focused on the doctor patient interaction, patient outcomes and satisfaction with the decision. Within each cluster, patients were also allocated randomly to consult with the doctor at one of three points in the study. The study comprised three phases. Phase 1 was pre-training. Phase 2 included training for half of the GPs and the other half in RC. In phase 3, each GP received training in the other element making them fully trained in both. The authors argued that in this way, the design offered the greatest potential to gain understanding about the effects of each form of training alone and in combination and if the sequence of skill acquisition was important. A further randomisation allocated patients to attend either in usual surgery time or in a research clinic- audio taped, including fewer interruptions and more time for each consultation (up to 15 minutes each).

SDM training involved GPs attending two workshops where standardised and previously piloted skill development process was used. SDM competences were described and demonstrated by means of consultation simulation and pre-prepared scenarios involving the four study conditions. RC also involved attendance at 2 workshops, and the aids consisted of tabulated data and visuals displays of risk estimates for the four study conditions. Patients with one of four conditions (menorrhagia, atrial fibrillation, menopausal symptoms or prostatism) were invited by their GP to attend a "review consultation" to discuss their continuing treatment. Twenty GPs from 20 different practices in South Wales were recruited. Costs of training for both RC and SDM included time of trainers, of those being trained and of the simulated patients used as part of the training exercise. Information on prescriptions, investigations and referrals was obtained from questionnaires completed by each clinician at the review consultation.

Edwards (2004) reported statistically significant effects of the research clinic (which provided more time) in confidence in decision (p<0.01) and expectation

to adhere to chosen treatments (p<0.05). Anxiety scores approached significance for the RC intervention, as did expectation to adhere to chosen treatment for both interventions. No statistically significant effects of the risk communication or SDM interventions were seen on the whole range of patient-based outcomes.

However, Cohen (2004) concluded that due to the explanatory nature of the study, no assessment could be made on how training could affect the length of a consultation.

4.16.3.2 RCTs conducted outside the UK

Kinnersley (2007) [32] conducted a Cochrane review to find interventions which aimed to increase patient involvement by enabling patients to address their information needs within the consultation. Most of the RCTs were from the USA, 2 from Australia, 5 from the UK and one from the Netherlands. Most of the interventions were written followed by face-to-face coaching and videotape. Written interventions were in booklet or checklist form. The specific behaviours most encouraged were question-asking, raising concerns and requesting clarification or checking understanding.

Seventeen RCTs in the Kinnersley review (2007) looked at consultation length, 3 studies found a statistically significant increase (Hornberger, 1997; McCann, 1996 and Middleton, 2006) and 14 RCTs found no effect. Bolman (2005) found a decrease in the first consultation and an increase in the last consultation. The meta-analysis showed a small but not statistically significant increase in consultation length (SMD 0.10 95% CI -0.05 to 0.25).

Fifteen RCTs reported that the use of written materials during the consultation led to a small and statistically significant increase in consultation length (SMD 0.13, 95% CI 0.05 to 0.21).   There was a small and statistically significant increase in consultation length for interventions immediately before the consultation (SMD 0.16, 95% CI 0.03 to 0.29) compared to those carried out some time before (SMD -0.04, 95% CI -0.93 to 0.86).   RCTs with coaching

found a statistically non-significant increase (SMD 0.07 95% CI -0.07 to 0.20). In studies where there was additional clinician training there was little impact on consultation length for written and coaching materials. RCTs with clinician training SMD 0.17 (95% CI 0.01 to 0.32) compared to studies without clinician training SMD 0.17 (95% CI 0.10 to 0.24). It should be noted that of these seventeen RCTs only eleven of these related to our population of interest, the results for these are detailed below.

4.16.3.3   RCTs included in the Kinnersley (2007) [32] review

Hornberger (1997) conducted a two-armed, randomised trial of whether a self-administered pre-visit questionnaire enhanced awareness of patients concerns in the USA. They completed the Patient Concerns Form while waiting for their visit. This covered 25 items of concerns of five categories: desire for medical information, psychosocial assistance, therapeutic listening, general health advice and biomedical treatment. After the interview the patients completed a post-visit questionnaire which assessed their perceptions of the concerns addressed by the physician. The net effect of the intervention compared to the control group was a difference of 6.8 minutes (95% CI 0.4, 13.3) for total time in consultation. With most of the extra time spent discussing diagnoses (3.35 minutes, 95% CI 0.00 to 6.72) and in performing the physical examination (2.7minutes, 95% CI 0.5 to 4.9). The number of diagnoses increased by 30% in the intervention group compared to the control group (increase of 1.7 diagnoses per visit). Those in the intervention group had marginally higher satisfaction but this was not statistically significant except for overall quality of care (0.35, +/- 0.23, p=0.05).

Greenfield (1985) conducted a randomised controlled trial of an intervention to increase patient involvement in their care in the US. The intervention group received a treatment algorithm as a guide to help them read their medical record and a behaviour-change strategy. The participants were coached in

appropriate question-asking and negotiation of decisions. The intervention occurred in a 20 minute session before their regular consultation with their GP. The control group also saw a clinic assistant just before their regular appointment for a similar amount of time as the intervention group. They received a standard protocol of receiving information and review of ulcer disease and were given copies of these materials. They did not get to see their medical records. There was no statistically significant difference between groups in length of consultation after the interventions, both groups averaged 16 minutes per encounter. The time of the encounter before was 16.8, (s.d= 8.2) whereas the control group was 15.1 (s.d=7.6), a difference of 1.7 (95% CI -2.92 to 6.32). The time of the encounter after was 15.7 (s.d=6.7) for the intervention and 16.3 (s.d=9.7) for the control, -0.6 (95% CI -5.49 to 4.29). However, they differed in how they spent their time with the intervention patients spending more time involved in the interaction than controls.

Greenfield (1988) conducted a randomised controlled trial in a diabetic clinic in the USA. This intervention was the same as in Greenfield (1985) but delivered twice, before the initial and follow up consultations. There was no change in question-asking, patient satisfaction, knowledge or consultation length (30.30 s.d=13.80 intervention group versus 32.50 s.d=13.90 for the control group). Participation and the preference for active involvement increased.

Maly (1999) conducted a randomised controlled trial in a family medicine clinic in the US where patients received copies of their medical record progress notes and produced two main questions to ask their physician. Control group received health education sheets and made suggestion lists for their clinic care. The consultation length did not differ between groups.

Roter's (1977) randomised control trial in a family medicine clinic in the US involved 10 minutes with a health educator to identify questions from a question asking protocol. The participants were encouraged to ask questions and took a list in to the consultation. Question asking and patient satisfaction

increased and there was no difference between consultation length (29.90, s.d=12.70) vs 40.50 (s.d=92.70).

Thompson (1990a) conducted a randomised controlled trial in an obstetric and gynaecologist clinic in the USA. Participants received a question prompt sheet with instructions to write at least 3 questions to take to the consultation. Question asking increased and there was no change in patient satisfaction and consultation length 7.70 (s.d=2.90) vs 8.70 (s.d=4.70), 95% CI -0.26 (-0.80, 0.29).

Martinali's (2001) randomised controlled trial in the Netherlands used a checklist to prepare coronary patients for visiting their cardiologist. The short checklist which was to be completed at home was aimed towards structuring the exchange of information in the consultation and to concentrate on those issues that caused most concern to the patient. A brochure was also developed with instructions for the checklist. A brochure was also given from the Dutch Heart Foundation, which both groups received. The consultation length was 12 minutes (s.d=4.2) in the experimental group and 10.3 (s.d=3.8) in the control group, f=1.82, p=0.18.

Bolman's (2005) randomised controlled trial in cardiology clinics in the Netherlands involved a checklist of 49 questions on 10 issues (as Martinali 2001). This was mailed to the patient a week before each of three linked consultations. There was no change in patient satisfaction. Consultation length was reduced at first visit but increased at third visit (13.73, s.d=3.73 vs 16.22, s.d=5.84, 95% CI -0.49, -0.88, -0.10)

4.16.3.4   Other systematic reviews of RCTs

Harrington's (2004) [31] systematic review, which investigated how to improve communication in a consultation showed that studies overall found that by involving patients there was not a resultant increase in consultation length.

Five out of seven studies that included consultation length (and were our population of interest) found there was not a statistically significant increase in the length of consultation except for Hornberger (1997) and McCann (1996). All of these studies are in the Kinnersley (2007) review except for **McGee (1998)**, (a study conducted in the USA) which did not find any difference in consultation length.

The **Wetzels (2007)** [34] systematic review, which looked at interventions to improve older patients' involvement, reported findings related to consultation length. Only one of the three studies meeting the inclusion criteria of the review included consultation length (Cegala 2001). In **Cegala (2001)** the trained patients asked more medically-related questions, gained more information and provided more information than control patients. They did not verify information more than control patients and appointment length was not longer overall. (18.81 vs 22.59, p=0.46) and time engaged in talk 16.25 vs 14.41, p=0.68). This study was conducted in the USA.

4.16.3.5   RCTs (not included in any systematic reviews)

Loh (2007) [33] investigated the effects of a shared decision-making intervention in primary care of depression compared to usual care on adherence, satisfaction and clinical outcomes. The study was conducted in Sudbagen, Germany with primary care physicians as the unit of randomisation. The sampling frame (n=148) were sent a letter, 30 accepted the invitation to take part, 20 were randomly assigned to the intervention group and 10 to the control group, after drop out 15 and 8 were left respectively. The physicians had to recruit newly diagnosed depressive patients. The intervention physicians enrolled 263 patients and the control group 142. After their diagnosis the patients completed a questionnaire measuring patient involvement, depression severity and socio-demographic characteristics. After 6-8 weeks the patients completed a second questionnaire measuring adherence and treatment outcome. At the same time, the physicians rated their assessment of the patients' adherence. The shared decision-making intervention was then implemented with the

intervention group. The intervention was a multi-faceted program including physician training, a decision board for use during the consultation given to the patients after the consultation, printed patient information with specific encouragement to be active in the decision-making process. The physicians in the intervention group also completed modules on guideline-concordant depression care which included content on enhancing skills for improving the shared decision-making process. The outcomes measures were patient participation, treatment adherence, patient satisfaction, consultation time and clinical outcomes. There was no difference for the control group in patient participation before and after, whereas the intervention group had statistically significantly higher patient participation from pre to post intervention for the doctor facilitation scale ($p=0.001$) and there was an increase in the patient participation scale ($p=0.010$). There were no statistically significant differences in treatment adherence. Patient satisfaction was statistically significantly higher in the intervention 29.8 (s.d=2.7) than the control group 27.0 (s.d=3.6), $p=0.014$. There were no values taken for satisfaction before the intervention. There was no difference between groups for length of consultation 29.2 (s.d=10.7) versus 26.7 (s.d=12.5). Neither group had a statistically significant reduction in depression severity from baseline to post-intervention.

Hamann (2006) [86] conducted a randomised controlled trial which aimed to assess an intervention for shared decision-making in patients with acute schizophrenia. 107 patients from 12 acute psychiatric wards of two hospitals in Germany were included in the study. Before the consultation participants were given a talk on their treatment options and to prepare them for their GP consultation. A 16 page booklet decision aid covering the pros and cons of oral vs depot formulation, first vs second generation antipsychotics, psycho-education, and type of socio-therapeutic intervention. Trained nurses assisted the patients to work through the booklet and gave answers to any information requests. They had to write down their experiences with antipsychotic medicine and to indicate their preferences. They met with physicians within 24 hours of working through the decision aid. The control group received routine care. There was no difference reported in the time spent in individual

consultations as reported by the psychiatrists - mean 64 min/weeks for the intervention group compared to 60 min/weeks for the control group, p>0.05.

4.17 Cost–effectiveness of interventions to increase shared decision-making

The GDG were very aware of the importance of considering cost-effectiveness when reviewing interventions to increase shared decision making. The GDG were reassured that the systematic review on consultation length indicated that this did not necessarily increase as this was perceived by the GDG to be the area where cost effectiveness analysis might be important. The interventions recommended by the GDG generally involve improving communication and the targeting of information resources to the patients who need them.

While involvement in decisions can be considered a right the opportunity costs have to be considered. The process of shared decision-making can increase patient wellbeing by improving patient satisfaction with the consultation, as well as the wellbeing possibly of doctors and carers. This benefit is termed process utility in the literature [87] . However, any such benefits are likely to be relatively small in comparison to the health benefits emanating from the medical treatment. However, although many people may perceive involvement in their care decisions as beneficial, not everybody will value shared decision making in this way. As a result, a change in process utility may both be positive or negative. Although the current cost-effectiveness literature tends not to consider process utility, patient preferences in SDM can be investigated using discrete choice experiments including conjoint analysis. There are published studies which investigate the relative importance of features of a health care consultation. This evidence has not been formally reviewed as part this guideline, however, the following papers have been identified as examples of conjoint analyses. [88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104]

Increasing patient involvement in decisions may result in the agreement to prescribe and take a medicine, or equally, to not prescribe and take a different

medicine or no medicine. A programme that facilitates shared decision making between a HCP and a patient can be seen as an intervention to increase adherence to joint decisions including prescribed medicine, and thereby health of the population. The current evidence is very limited but it seems likely that the shared decision making process would improve cost-effectiveness by enabling patients to make a prediction of their individual valuation of harms and benefits and subsequently opt in or out of treatment. Theoretically it is likely to be of economic benefit to enable patients to decline a suggested prescription as it prevents people from accepting and filling prescriptions they might otherwise not have taken. No formal cost-effectiveness analyses of interventions to increase shared decision-making were found. Any analysis would have to include the effect on adherence and subsequent clinical outcomes. A discussion of the issues relevant to health economic evidence for interventions to improve adherence can be found in chapter 10.

5 Patients' experience of medicine-taking

5.1 Recommendations

Hyperlink to recommendations section Understanding the Patients Knowledge, Beliefs and Concerns about Medicines

5.2 Introduction

If health care professionals are to facilitate patient involvement in decisions about medicines it is helpful and necessary to understand how patients approach the taking of medicines, in particular the ongoing appraisal of medicines that continues after a consultation. Investigation into why patients do not take medicines as prescribed indicates that the decision to take medicines and the continuing taking of medicines should be considered as a complex behaviour [1].

5.3 What are the barriers and facilitators for individuals in medicine-taking

Related references	Evidence statements (summary of evidence)
Pound (2005)[7]; Munro (2007) [105]; Mills (2006) [106]; Carrick (2004) [107]; Deegan (2005) [108]; Lewis (2006) [109]; Cooper (2002) [110]; Ogedegbe (2004) [111]; Lukoscheck (2003) [112]; Wilson (2002) [113]; Bollini (2004) [114]; Adam (2003) [115]; Scotto (2005) [116]; Alfonso (2006) [117]; Sidat (2007) [118]; Lewis (2006) [109]; Pyne (2006)	Patients wish to minimise medicine intake where possible. They may wish to do this to decrease adverse effects and potential for addiction, to make the regimen more acceptable or for financial reasons. Patients may decide to use prescribed medicine to alleviate symptoms or strategically, to replace or supplement medicines sometimes or all the time with non-pharmacological treatments.

Patients will commonly evaluate prescribed medicines by trying out the medicines and |

[119]; Kikkert (2006) [120]; Vinter-Repalust (2004) [121]; Campero (2007) [122]; Reid (2006) [123]; Elliott (2007) [124]; Aronson (2005) [125]; Garcia Popa-Lisseanu (2004) [126]; Erwin (1999) [127]; Mutchler (2007) [128]; Lawton (2005) [129]; Morgan (2005) [130]; Ring (2007) [131]; Campero (2007) [122]; Chen (2007) [132]; Gascon (2004) [133]; Vermeire (2003) [134]; George (2003) [135]; Fraenkel (2007) [136]; Field (2006) [137]; Badger (2006) [138]; Givens (2005) [139]; Attebring (2005) [140]; Nair (2007) [141]; Gordon (2007) [142]; Bajcar (2006) [143]; Taylor (2002) [144]; Enriquez (2004) [145]; Gray (2006) [146]

weighing up the costs and benefits. They will consider adverse effects and acceptability of regimen. They may stop the medicine and see what happens and obtain information from non-medical sources and observe the effect of medicines on others.

Both subjective and objective indicators may be used to evaluate medicines.

Patients do not generally disclose their beliefs and change of regimen to HCPs.

Patients may not be able to recognise the difference between effects of medicine and effects of disease and have difficulty in evaluating long term preventative medicine where there are no symptoms.

Patient on multiple medicines may make choices between medicines.

5.3.1   Evidence to recommendations

The GDG discussed the appropriate research methodology to provide evidence of patients' actual medicine-taking behaviours. The GDG considered it important to provide health care professionals with evidence of how patients actually use medicines to sensitise professionals to issues that may be relevant for discussion with individual patients. The GDG accepted the use of qualitative evidence for this and considered the Pound synthesis provided the type of evidence they were looking for. The description of patient behaviours and factors influencing patients medicine-taking behaviours were used to inform the recommendations about exploring patients' beliefs and concerns,

the type of information that patients' may require and to describe common medicine-taking behaviour that healthcare practitioners might wish to discuss with patients.

5.3.2   Methods of the evidence review

Searches of the literature revealed a large number of studies that set out to explore patients' experience of medicine taking. The majority of these studies are qualitative studies. One of the current challenges in qualitative research is how to bring together the findings from individual qualitative studies. One approach is to present a narrative of these studies describing their findings individually. More recently the field of qualitative synthesis has attempted to synthesise the findings from different studies into a common set of findings that includes the findings from individual studies but that may also provide additional levels of understanding that may not be apparent when each study is looked at individually. A synthesis of medicine-taking has already been conducted using a meta-ethnography [7]. The Pound (2005) [7] review is methodologically sound and systematic synthesis developed by a panel of experts within the field of medicines adherence. Following discussion with the GDG it was agree that rather than conduct an alternative summary or synthesis of the qualitative studies of patients experience of medicine-taking we used the synthesis as the basis for our evidence review. The findings of the synthesis were updated by searching for evidence published since the review was conducted and a narrative summary of these presented. The GDG requested additional search for systematic reviews.

5.3.3   Evidence review

Pound (2005) [7] aimed to conduct a synthesis of qualitative studies of lay experience of medicine-taking. The study was part of a Health Technology Assessment project to evaluate meta-ethnography as a method of synthesizing qualitative research studies of health and health care. This narrative has used the paper published in Social Science and Medicine [7]. The authors of the HTA report kindly allowed us to read a draft copy of their report for the HTA which primarily concerned the detail of their methodology. Studies

using both qualitative methods of data collection and qualitative methods of data analysis and published in English were included. Studies published between January 1992 and December 2002, were eligible for inclusion. Medline, Embase, Cinahl, Web of Science, Psychinfo and Zetoc were searched. The electronic search was supplemented by extensive hand-searching. Papers were appraised for quality using a version of CASP 1988 criteria. Thirty-eight papers were included in the synthesis. Papers were organised into medicine groups. The initial synthesis brought together papers looking at similar medicine/disease groups and these findings were then synthesised. The medicine groups were antiretroviral therapy, anti-hypertensive medicine, psychotropic medicine, proton-pump inhibitors, asthma, miscellaneous medicines and medicines in general.

The paper reports a summary of the findings of the individual studies and the results of the synthesis of these studies. The authors developed the concept of 'resistance' to medicines to describe lay-peoples' response to medicines. One of the main conclusions of the synthesis is that people do not take medicines as prescribed because of patient concerns about medicines themselves. Their interpretation is that nonadherence is not necessarily a result of failures from the professionals, patients or systems, but because of concerns about the medicines themselves. Drawing on issues such as patient reports of testing for adverse effects; worries about dependence; the potential harm from taking medicines on a long term basis; and issues with disclosure and stigma, the authors' conclude that many patients 'resist' the taking of medicines. Patients can be described as 'acceptors' of medicines, some uncritically, others following their own enquires and experimentation. People's medicine-taking may change with different medicines and the illness in question, which illustrates the relative nature of the concept of "resistance". Those that may "resist" a certain type of medicines may "accept" a different medicine.

The findings of the synthesis fell into three parts (1) the way people evaluate their medicines and the difficulties they encounter in doing this (2) the interaction between medicines and patient identity (3) the ways people take

their medicines. The themes that make up each part are listed under each heading.

5.3.4 The evaluation of medicines and the difficulties encountered by people in evaluating medicines

Trying out the medicines and weighing up the costs and benefits
The most common way of evaluating medicines was to try it out and weigh up the benefits of taking it against the cost of doing so. The majority of the studies focused more on the problems associated with medicine and less on the benefits of medicine, but it was clear that people had hope that their medicines would help with the symptoms; avoid relapse and hospitalisation; for minimisation of disease progression or for prevention of future illness.

Adverse effects
Adverse effects were a key criterion in the evaluation of medicines. This was found in several studies including those about treatments for cancer, rheumatoid arthritis, asthma, diabetes, schizophrenia and digestive disorders. Adverse effects were very prominent in studies of patients taking anti-HIV medicine. The frequency and nature of adverse effects experienced by these patients, particularly as adverse effects were severe and unpredictable, resulted in distrust and fear of the medicines. These adverse effects affected social activities, relationships and work.

Acceptability of regimen
People reported the evaluation of the suggested regime in terms of how it fitted in with daily schedules and life in general. The frequency of doses and number of pills was also a challenge, as also taste, smell, size and shape of the pills. Regimes that required disruption of schedules resulted in patients reporting that they were no longer in control of their lives and people varied as to whether they fitted the world around their regime or resisted the demands of the regime and missed doses.

Weighing and balancing

A process of weighing and balancing was carried out by people, mainly where the advantages of treatment in terms of symptoms or effect on disease was balanced by side effects and disruption. Adverse effects and disruption would lead people to question if it was worth taking medicine or not.

Stopping the medicine and seeing what happens

In some cases, patients test the medicines by either changing the doses or stopping the medicine as to observe what happens. Some authors suggest that this process can either be explicit or subconscious and tends to occur more frequently in long term conditions.

Observing others, obtaining information

Patients used a variety of sources of information with some patients relying more on their observations of how other people dealt with medicines such as HIV medicines rather than the advice/information given by the doctor. People use a variety of sources of information (e.g. internet, books and support groups) as well as that provided from their GPs.

Objective and subjective indicators

People used both objective and subjective indicators to evaluate efficacy of medicine. In the studies in the synthesis, blood pressure monitoring appeared to be used widely as a means of evaluating efficacy of antihypertensive medicine. The perception of symptom minimisation could be as important as objective indicators such as an increase in T-cell count in the case of HIV patients.

Gender differences in evaluating medicines

Some studies suggested that women with HIV do not belong to certain social networks like gay men or injecting drug users and thus could be less informed about the medicines. Also, some women were reported to show scepticism towards the medicines used for HIV with arguments that the clinical trials had not been conducted with women.

Difficulties with evaluating medicines

In some studies it was noted that patients could not distinguish between the effects of their illness from the effects of the medicine. This could even lead to patients rejecting treatments mistakenly. Other authors pointed out that evaluation can be dependent on the individuals understanding of how a medicines works and its function and this can be difficult for certain people due to lack of information and understanding. This is particularly relevant in the case of preventative medicine, as there are no immediate symptoms that can be used as indicators of efficacy.

Worries about medicines that lay testing and evaluation cannot resolve

Fear of dependency and tolerance were pointed out as issues for patients. Fear of addiction was reported when taking psychotropic medicines and general concern over taking medicines on a long term basis was present with hypertensive medicines. Some authors noted that those who worried over the long term effects of medicines were those most likely to change their regimen to the lowest possible dose.

5.3.5   Medicines and identity

Non-acceptance

Since taking medicine is equated with having an illness people may not take medicine if they do not accept their illness. This was particularly strong in the asthma studies in the synthesis. The relationship with acceptance of disease was, however, complex with some patients using medicines to keep their problem under control and downplay its significance. In the case of neuroleptic medicine and HIV medicine an acceptance of the diagnosis was crucial in determining whether the patient would take their medicine as prescribed. Medicine was seen as a reminder of illness.

Disclosure and stigma

People with potentially stigmatising illnesses such as HIV and mental health problems were particularly concerned that their medicines marked them out as individuals with those particular health problems. This could lead to avoiding taking medicine in public and either postponing or foregoing their

medicine intake. Some people were reported to not initiate treatment which would reveal them as having HIV. Patients with mental health problems also reported feeling stigmatized by their intake of medicines, and some felt ashamed.

5.3.6   Ways people take their medicine

Motivation to minimise intake

The majority of studies illustrate how people wish to minimise their intake of medicines with patients spontaneously reporting dislike of medicines to researchers. This was also true in the case of medicines commonly reported as being overused by patients, such as benzodiazepines.

To decrease adverse effects and addiction

People often reduce or skip doses, or take tablets separately rather that all at once. Others may temporarily stop their medicine intake as a way of cleansing their body and minimise toxicity.

To make the regimen more acceptable

This section related to how people modified their regimen in order to fit with their daily schedule, alleging that to have some clinical gain, complete adherence was not required. Other argued that the optimum regimen was not known anyway, and that strict adherence was not possible.

For financial reasons

Some people were reported to have decreased their doses as they could not afford the prescribed amounts.

Using medicine symptomatically

Some patients were reported to use medicines accordingly to symptoms displayed. Patients associated symptoms with their medical problem and when these symptoms indicated that the problem was not controlled they would take their medicines. An example was symptoms of tiredness or weakness in treatment for high blood pressure. People with rheumatoid arthritis modified their doses according to their symptoms as did patients on neuroleptic medicines.

Using medicine strategically

People adjusted their dose or did not take their medicine when planning to drink alcohol as they feared possible interactions. This was also reported for those on neuroleptic medicines and antihypertensive medicine. PPIs were also altered according to what people planned to eat.

Replacing or supplementing medicines with non-pharmacological treatments

In varying ways, people often complemented their treatment with home remedies. On a more specific level, some patients who worried about the harmful effects of medicines would sometimes take a break and use natural remedies for a certain period.

Doctor-patient communication about regimen modifications

Some patients reported being scolded by their doctors if making their own decisions about their care. Rather than confronting them, they would then switch doctors. Also, many patients do not reveal their beliefs to the doctors, but once outside the surgery and in control, people would then change or refute their regimen. Some authors noted that patients who had changed their regimen would not disclose this to the HCPs due to previous experience of coercion or recognition of their powerless position. Authors argue that as patients self-regulate anyway, doctors need to recognize this and even support them in the process, as well as helping people feel in control.

Imposed compliance

One issue that was found exclusively in studies relating to mental health was that of 'imposed compliance'. Patients with mental health problems felt surveyed for signs of ill health and under pressure or even coercion from friends, relatives and health care professionals to take medicines. Patients felt that medicine was used to make them acceptable to society and was part of an unwritten social contract that required the taking of medicines to allow patients to be acceptable to the community.

5.4 Update of qualitative evidence synthesis - Pound 2005 synthesis

5.4.1 Methodology of update

The aim is to update the synthesis of qualitative evidence of medicine-taking in a similar methodological approach as when updating a Cochrane review. The titles and abstracts of records retrieved by the searches were scanned and any potentially relevant publications obtained in full text. The studies were reviewed to identify the most appropriate evidence to help answer the key questions and to ensure that the recommendations are based on the best available evidence. Qualitative synthesis is considered a process where the analysis of a number of qualitative studies may result in new findings not contained in the individual studies. It was felt therefore inappropriate to do additional synthesis to that undertaken by Pound et al. This update is a narrative review which discusses the studies found in the update particularly where the findings add to the existing synthesis.

Types of studies - studies with both qualitative methods of data collection and analysis published in English.

Types of participants - people aged above 16 years prescribed medicine for a medical condition (3 studies included in the synthesis relate to children and/or adolescents).

Duration of studies - there was no limit on the duration of studies.

Possible challenges - One of the first challenges of the process of developing a systematic review on qualitative evidence is how to find the evidence. Qualitative evidence is catalogued on a wide range of databases or sometimes not at all and indexes and search filters require substantial improvement if they are to be rigorous and systematic. Secondly, is the lack of agreement of appropriate methods for appraising the quality of qualitative evidence. We will use the same CASP criteria as those used in the original synthesis.

5.4.2 Evidence review from update searches

Update searches

Our update searches produced 381 references. Based on abstract information, eighty five studies were ordered. Further exclusions were made if the study turned out not to be relevant for the topic, or did not have qualitative data collection and analysis. CASP criteria were used to assess the quality of the studies. The details of all the studies are in Appendix C. Forty-five studies were included in the update. The studies covered a wide range of medical conditions and patient groups but did cluster around long term conditions. Twelve were concerned with HIV medicine, 8 with medicine for psychiatric conditions and 4 for patients with diabetes. Five studies focused on patients from low income and/or ethnic groups. A shift could be seen in that most recent studies discussed the issue of patient-health care professional communication more explicitly than those included in the Pound synthesis. Many papers, as in the Pound synthesis, accepted a medical paradigm that medicine-taking was a good thing and some sought to understand patients' beliefs and experience with a view to improving adherence. Patients' readiness to negotiate with health care professionals and to disclose their medicine-taking behaviour to health care professionals was discussed [147] as was the challenges facing health care professionals in supporting the integration of patients' needs and preferences [148]. In general the findings fitted well into the categories elaborated in the Pound synthesis although studies often developed their own terminology and categories. As described in the Pound synthesis many studies did not reference each other. The findings in this update are described under the themes as described in the Pound synthesis i.e. (1) the evaluation of medicines and the difficulties people encountered in this, (2) medicines and identity and (3) the ways people take their medicine.

5.4.2.1 The evaluation of medicines and the difficulties encountered by people in evaluating medicines

The findings of the update searches were similar to the findings of the Pound synthesis in how patients evaluated medicines. The themes of trying out the

medicines and weighing up the costs and benefits were present as well as the importance of adverse effects and the acceptability of the regimen. The studies elaborated different terminology. **Carrick (2004)** [107] developed a core concept of 'well being'. The study was an interview study of 25 adults taking antipsychotic medicine. The findings were that patients sought to maximise 'well-being' which was normality of function, feeling and appearance. 'Well being' was defined personally by patients and was their goal in taking treatment. The achievement of well-being was a net effect of symptoms and side effects. Some patients preferred the effects of their disease to the side effects of treatment. This was achieved by interplay of evaluating treatment, managing treatment and patients' understanding of the situation. Patients considered medicine in the context of their beliefs about their illness and its causes. While the maximising of 'well-being' was relevant for all patients interviewed there was a spectrum of behaviour in relation to how active the patient was in engaging with their doctors and talking through their views about medicine. **Deegan (2005)** [108] again in the field of psychiatric problems developed a concept of 'personal medicine'. She interviewed 29 patients with psychiatric problems and considered that psychiatric medicines are considered in relation to 'personal medicine' i.e. non-pharmaceutical activities that gave meaning and purpose to life and that serve to raise self-esteem, decrease symptoms and avoid unwanted outcomes. Examples of personal medicine were the ability to work, and to parent appropriately and to engage in social activities. Her analysis was that medicines that conflict with patients' 'personal medicine' are unlikely to be used by patients.

Balancing the benefits of medicine against the side effects of treatment was a theme also in studies of patients on medicine for HIV**. Lewis (2006)** [109] interviewed patients who were 100% adherent to HAART and found that they performed a trade off between the benefits and side effects of medicine. In this sample of adherent patients the interviewees reported that they did not have many other options for treatment and HAART was important in keeping them well. **Cooper (2002)** [110] interviewed 26 patients who had declined HAART treatment and found that they used their own interpretations (which

often differed from professional interpretations) of indicators such as CD4 counts to inform their decision, preferred non-pharmacological treatments and also found the lack of symptoms an issue in considering treatment. The paper uses the concept of patients' perceived 'personal necessity' of treatment as a factor in their decision. Patients also had concerns about medicines from previous personal experiences or from seeing and talking to others taking HIV medicines.

The methods by which people evaluate medicines and the difficulties experienced by patients in doing so were present in the studies. **Ogedegbe (2004)** [111] interviewed 106 African –American patients in urban primary care clinics. Patients had difficulties in evaluating treatment due to the lack of symptoms of raised blood pressure. Many used their own indicators to consider if and when they should take any treatment. **Lukoschek (2003)** [112] interviewed 92 African-American patients about their beliefs and attitudes to hypertension and anti-hypertensive medicine. Patients held differing understandings of high blood pressure and hypertension. Patients' beliefs about problem influenced their approach to treatments including diet, exercise and medicine. Patients' weighed beliefs about advantages of medicines against the side effects and many patients preferred herbal and alternative remedies. Patients with HIV interviewed for the study by **Wilson (2002)** [113] found it difficult to understand and assess their medicine as they did not know whether any symptoms were related to their disease or the medicine. **Bollini (2004)** [114] in a study of patients taking anti-depressant medicine indicated that patients would test treatment by stopping once they felt better to see what would happen and if they really needed the medicine.

For HIV patients to derive benefit from HAART medicine, high adherence to the prescribed regime is required. The acceptability of the regimen and fitting it into schedules was a significant issue in all studies which examined patients' experience of taking HAART medicine. **Adam (2003)** [115] interviewed patients who were taking HAART but found the required schedule difficult and altered the dosing regime and associated eating rules to fit the regime into their schedules. This paper concludes that the nature of HAART medicine and

its regime should be seen as the problem with this medicine and nonadherence not seen as a patient problem.

5.4.2.2 Medicines and identity

The meta-ethnography synthesis indicated that for many patients the taking of medicines interacted with issues of identity. Non–acceptance of diagnosis and issues around disclosure and stigma were significant issues in studies found in Pound synthesis. Medicines challenged patients to consider themselves as someone with a disease or could provide external evidence of a stigmatizing disease. These issues recurred in the studies included in the update. **Scotto (2005**)[116] interviewed 14 patients who had required hospitalization for a relapse of heart failure symptoms. In this sample the acceptance of the diagnosis of heart failure resulted in an altered self-image for patients but this acceptance and its integration into patients' lives was an important part of managing medicine. Behaviours to support adherence worked when the illness and its management could be integrated into ordinary life. **Alfonso (2006)** [117] interviewed 15 people who were HIV positive who were not taking medicine and explored their reasons not to take medicine. Many had prior experience of taking HAART. Not taking medicine allowed some to deny that they were HIV positive. For some either taking HIV medicine per se or the occurrence of side effects of this treatment risked exposing their HIV status. Many already felt isolated and separate and did not want to exacerbate this**.** Similar issues of taking HAART were reported in an interview study by **Sidat (2007)** [118] where patients delayed in starting treatment while dealing with issues of identity and denial. **Lewis (2006)** [109] interviewed 13 patients who were known to be 100% adherent to HAART treatment and a prominent theme in this sample was transcending their identity as someone with HIV which for the patients was associated with feelings of self-blame and moving on from that to take control of their health and its' maintenance. In an interview study by Wilson and colleagues [113] issues of identity are more dynamic and are part of an ongoing appraisal of medicines and medicine taking. **Pyne (2006)** [119] explored explanatory models of schizophrenia and treatments for schizophrenia held by professionals and

patients to provide both provider and patient perspectives. There were significant differences between providers and patients in models of disease, its causes and required treatments. Stigma was identified as a problem by patients but not providers. **Kikkert (2006)** [120] explored views of patients with schizophrenia, their carers and professionals on medicine for schizophrenia. A significant barrier for this patient group was the social consequences of extra-pyramidal side effects of medicine. Patients taking antidepressant medicine also reported difficulty in accepting the diagnosis and therefore the need for treatment **Bollini (2004)** [114]. Patients with diabetes complained of a stigma of been seen with and using treatment for diabetes in a study by **Vinter-Repalust (2004)** [121]. For these patients coming to terms with the identity of being a patient with diabetes was a significant challenge. **Ogedegbe (2004)** [111] found that African–American patients reported difficulty coming to terms with a diagnosis of hypertension as a significant problem in taking anti-hypertensive medicine.

5.4.2.3 *Ways people take their medicine*

The ways in which patients take their medicines were similar in the update studies as in the Pound synthesis. Patients changed their medicines and used medicines in strategic ways but did not necessarily disclose this to health care professionals **Deegan (2005)** [108]. In the sample interviewed by **Ogedegbe (2004)** [111] the cost of prescriptions and the effort involved in getting prescriptions reordered and refilled meant people did not take their medicine continuously. Studies of patients prescribed HIV medicine similarly indicated patients making adjustments to their regimes in keeping with their own beliefs and experiences and not reporting these to health care professionals **Campero (2007)** [122].

In general patients would not report their treatment modifications to health care professionals unless they saw themselves as expert patients. The ubiquity of patients' alteration of their regimes is indicated by the findings of **Aronson (2005)** [125]. This was a small study of 11 patients, who were described as completely adherent to medicine. They were all prescribed short

term courses of antibiotics and all patients took all the medicine. These patients however did alter the timing of doses to fit in with their schedules. Doses were forgotten and then taken when remembered. **Wilson (2002)** [113] describes HIV patients making decisions about how they take their medicine almost on a dose-by dose basis. This was for a number of reasons and in this study patients' medicine-taking behaviours are described as a result of reconciling incompatibilities which included illness beliefs, the difficulty of the regime and its impact of life. Patients generally described themselves as adherent to health care professionals. **Reid (2006)** [123] describes the strategic use of diuretic medicine by patients with heart failure- patients changing the timing of medicine or omitting the dose according to social and other activities.

5.4.2.4   Additional findings from update search

The findings of the qualitative studies included in the update of the Pound synthesis (2005) fitted largely within the themes found in the original synthesis. A finding not elaborated in the synthesis and not found in other update studies was medicine-taking experience and behaviours in older adults on complex regimes. **Elliott (2007)** [124] interviewed 20 patients aged 67-90 about their experience of medicine-taking. Patients were all members of one HMO and took 4-12 medicines. The researchers were particularly interested in how patients on multiple medicines make decisions about medicines. The general findings from the study did not differ from themes found in synthesis – patients wished to minimise medicine overall, they stopped and started medicine to take a break from medicine, to check if they were working, to determine the cause of side effects and generally did not disclose this behaviour to their physicians. The patients interviewed did report having made choices between which medicines they would decide to take, this included choices between medicines for different disease and choices within diseases. When choosing between medicines for different diseases patients chose to take the medicine for the disease they feared most or that which gave symptomatic relief. Choices otherwise were influenced by symptom control, side effects, medicine cost, negative health experience, illness beliefs and acceptability of medicine (i.e. taste etc). Illness beliefs

dominated more general factors such as influence of family, friends, health providers and the media. Complexity of regime did not affect choice. Cost was a factor even when not related to financial hardship, and patients appeared to resent the cost of medicines. Choices were generally influenced by one dominant factor and less likely to be a result of analysis of multiple factors.

Two studies reported on structural issues that interfered with patients' ability to appraise medicine and to receive the information they required to do this. **Garcia Popa-Lissenau (2004)** [126] reported on the difficulties patients from low incomes with rheumatological disorders had in physically accessing appointments with professions. **Mutchler (2007)** [128] reported how for non-English speaking Latinos in the US the difficulty in engaging with health care professionals results in reduced information available to those patients and poorer relationships with professionals which of itself could reduce trust in treatment.

5.4.2.5   *Experience of medicine-taking of minority groups in UK*

We specifically searched for papers examining experience of patients from minority groups in the UK. Overall their use and experience of medicines was similar to that already described in the evidence review. One additional finding in **Erwin (1999)** [127] was a belief by patients of African origin that they had different physiology from white people and that medicines used for treatment of HIV might not be appropriate for them and that they were being discriminated against. This was an issue also raised by African American patients interviewed. **Sidat (2007)** [118] found that this patient group were also often involved in church activities and some churches were against use of medicine. **Lawton (2005)** [129] explored the perceptions of diabetic patients of Indian and Pakistani origin of taking oral hypoglycaemic medicines. These patients' beliefs and use of medicines was influenced by their experience of the health system in their country of origin. They distrusted this system and admired the NHS but consequently considered that the medicines available in the UK were likely to be stronger and more efficacious than those available in their country of origin and so they reduced dose and sought to balance effect of medicines by taking in 'strong' foods. People of African origin living in South

London were interviewed about their use of malaria prophylaxis **Morgan (2005)** [130]. One of the factors influencing use of anti-malarial was the practice of leaving medicines in Africa for family members.

5.5   Systematic reviews of barriers and facilitators for individuals in medicine-taking

5.5.1   Methods of the update

The GDG requested an additional search for any further systematic reviews of barriers and facilitators for individuals in medicine taking. The search strategy used for the Pound updates searches was applied to this review together with a systematic review filter. The titles and abstracts of records retrieved by the searches were scanned and any potentially relevant publications were obtained in full text. Cross-referencing of all the studies was undertaken to ensure that the search is as comprehensive as possible. The studies were then reviewed to identify the most appropriate evidence to help answer the key questions and to ensure that the recommendations are based on the best available evidence.

Types of studies: Systematic reviews.

Types of participants: people aged above 16 years prescribed medicine for a medical condition.

Duration of studies: no limit on duration of studies.

5.5.2   Evidence review

The search for systematic review of barriers and facilitators of medicine-taking produced two eligible reviews in very diverse patient populations. No systematic reviews examining statistical associations between patient reported factors and actual medicine-taking were found. The systematic reviews that were found examined medicine-taking in particular population subgroups – patients with TB and patients with HIV on retroviral treatment.

Although there was potential overlap in terms of type of studies informing a synthesis between medicine-taking in these areas and medicine-taking in the Pound synthesis there was little overlap in papers included in each synthesis highlighting the issues raised by authors of Pound synthesis about difficulty of locating qualitative literature.

The first of these **Munro (2007)** [105] is a review of qualitative studies which aimed to understand the factors considered important by patients, caregivers and health care providers in contributing to TB medicine adherence. The authors used meta-ethnography as in Pound synthesis. The majority of the studies in this review were conducted in developing countries. The emphasis on adherence and inclusion of carers and health care providers' perspectives as well as the methodology resulted in an analysis which included structural factors that influence patients' medicine-taking as well as patient factors.

The primary themes that emerged from the included studies were: 1) Organization of treatment and care including access to care, treatment requirements and relationship with the provider; 2) Interpretation of illness and wellness; 3) Financial burden including impact on work, cost of treatment, general poverty; 4) Knowledge attitudes and beliefs about treatment; 5) Law and immigration; 6) Personal characteristics and adherence behaviour including substance abuse, gender ,religion, motivation; 7) Side effects; 8) Family, community and household influence.

A systematic review by **Mills (2006)** [106] examined patient reported barriers and facilitators to adhering to antiretroviral therapy. This analysis included 37 qualitative studies and 47 surveys using structured questionnaires or structured interviews. Seventy-two studies were conducted in developed countries. Fifty-six were from the US and only 3 from the UK. A systematic approach was taken to extracting themes from the qualitative studies and synthesizing the quantitative data and pooling the results. Briefly the authors extracted themes from the qualitative studies and then reviewers examined the quantitative surveys to determine if the same issues had been addressed in the surveys. The authors used their own criteria to assess the surveys and

these related to the development process and face validity of the questionnaire and the population surveyed. The authors used the prevalence of themes as reported in the surveys for their statistical analysis. This technique is called meta-study and is one of a series of methods being developed to bring together findings of qualitative and questionnaire studies.

Barriers identified in both economic settings (developed and developing world) included: fear of disclosure, concomitant substance abuse, forgetfulness, suspicions of treatment, regimens that are too complicated, number of pills required, decreased quality of life, work and family responsibilities, falling asleep and access to medicine. Important facilitators reported by patients in developed nation settings included having a sense of self work, seeing positive effects of anti-retroviral medicines, accepting their seropositivity, understanding the need for strict adherence, making use of reminder tools, and having a simple regimen. In a further study of adherence rates in sub-Saharan Africa and North America [149] Mills comments that the most prevalent barriers to adherence in sub-saharan Africa are cost, not disclosing HIV status to a loved one or fear of being stigmatised, alcohol abuse and difficulty in following complex medicine regimens.

6 Information for inpatients and practitioners when patients are transferred between services

6.1 Recommendations

Hyperlink to recommendations section Providing Information

Hyperlink to recommendations section Communication Between Healthcare Professionals

6.2 Introduction

Patients are frequently started on medicines when in hospital as an inpatient or when attending outpatient clinics. Transitions between care settings have been recognised as a time when potential errors in medicine can occur. NICE and the National Patient Safety Agency (NPSA) have recently produced joint guidance on medicines' reconciliation when adult patients are admitted to hospital (www.NICE.org.uk/PSG001). Literature reviews suggest unintentional variances of 30-70% between medicines which patients were taking before admission and those prescribed on admission. The GDG considered that patients have the same rights to information and choice regardless of setting but acknowledged that this is not always possible when patients are acutely unwell.

6.3 What information regarding medicines should be provided for patients and practitioners when patients are discharged from secondary care?

6.3.1 Evidence to recommendations

The GDG recognised that medicines may be initiated in hospital settings in emergency situations and when patients are unwell. They recognised that in these situations discussions of details of medicines may not be possible. However as patients' condition improves and patients are prepared for discharge they should be offered a full explanation of their medicine. This explanation should allow patients to make informed choices about their continued use of the medicine prescribed. The experience of the GDG was of considerable confusion and lack of information provided to patients and to subsequent providers of care when patients are discharged. Difficulties arise not only in knowledge of what medicines have been prescribed for patients but what information patients have been given about their illness and medicines. The GDG based these recommendations on professional opinions and information from expert sources.

6.3.2 Methods of the evidence review

The evidence review is a narrative review. The GDG requested a review of available guidance and reports with a particular emphasis on those where patients' rights to information and involvement were given priority.

6.3.3 Evidence review

The Academy of Royal Medical Colleges is currently preparing consensus guidance on what should be included in hospital discharge summaries. This guidance which will include advice on information about medicines will be available late in 2008. The WHO produced a report in 2007 on Assuring Accuracy of Medicines at Transitions of Care (www.jcipatientsafety/org/). The emphasis on reports and guidance about medicines reconciliation is on the

reduction of medicines errors. Patients' rights to information and involvement in decisions about medicines are not the primary concern of these reports. The WHO report does however state that effective involvement of patients and families in medicines reconciliation is vital to reducing errors. They suggest that:

- The patient is in the best position to be aware of all the medicines prescribed by multiple caregivers.
- Consideration should be given to asking patients to put all their medicines in a bag and bring it with them whenever going to the hospital or a doctor visit.
- Patients, family, and caregivers should be encouraged to keep and maintain an accurate list of all medicines, including prescription and non prescription medicines, herbal and nutritional supplements, immunisation history, and any allergic or adverse medicine reactions. These medicine lists should be updated and reviewed with the patient/family/caregiver at each care encounter.
- Patients should be taught about the risks of medicines, both individually and in combination, with particular attention to patients on multiple medicines prescribed by multiple caregivers.

7 Assessment of adherence

7.1 Recommendations

Hyperlink to recommendations section Assessing Adherence

7.2 Introduction

Many patients take medicines over long periods of time and discussions about these medicines need to consider the patients experience of taking the medicine. This includes an assessment or discussion about whether or not the patient is taking the medicine and if they are doing this exactly as prescribed or in some other way.

A number of ways of assessing adherence have been developed. These can generally be described as direct methods or indirect methods. Direct methods are examinations of blood, urine or other bodily fluids for the presence of the medicine or a metabolite. Indirect methods do not measure the presence of the medicine but use methods such as self report from patients, pill counts, prescription reordering, pharmacy refill records, electronic medicine monitoring and therapeutic effect to form an assessment of adherence. In the context of routine clinical practice and of involving patients in decisions about medicines the GDG considered that indirect methods were the most commonly used. Self-report is the most available method for reporting adherence in a clinical context. The GDG wished to consider the advantages and disadvantages of self report in routine clinical practice to recommend how it should be used by practitioners. We conducted an evidence review to explore specifically the advantages and disadvantages of self-report for assessing adherence. Other types of measures of adherence were not explored.

7.3 What are the advantages and disadvantages of self-report in assessing patient's adherence?

Related references	Evidence statements (summary of evidence)
Advantages	
Hawkshead (2007) [150]; Gagne (2005) [151]; Paterson (2002) [152]; Miller (2000) [153]; Turner (2002) [154]; Farmer (1999) [155]; Bender (1997) [156]; LaFleur (2004) [157]; Rand (1994) [158]	Self-reporting is the most simple and inexpensive method of measuring adherence.
Miller (2000) [153]; Farmer(1999) [155]; Paterson (2002) [152]; Bender (1997) [156]; Rand (1994) [158]	Self-reporting is quick and easy to administer, avoiding the use of sophisticated methodology or equipment.
Hawkshead (2007) [150]; Bender (1997) [156]	Self-reporting methods which are validated can feasibly be used in clinical settings.
Hawkshead (2007) [150]; Paterson (2002) [152]; Farmer (1999) [155]; Hecht (1998) [159]; Bennett Johnson (1992) [160]; George (2007) [161]	Self-reporting can identify those who are nonadherent. It is most likely those reporting nonadherence are being truthful.
Hawkshead (2007) [150]; Miller (2000) [153]; Rand (1994) [158]; Bennett Johnson (1992) [160]	Self-reporting can gather social, situational and behavioural factors including revealing patterns of medicine use and what leads to non-compliance.
Disadvantages	

George (2007) [161]; Hawkshead (2007) [150]; LaFleur (2004) [157]; Turner (2002) [154]; Miller (2000) [153] Hecht (1998) [159]; Bender (1997) [156]	Self-reporting has the problem of over-estimating adherence.
Hawkshead (2007) [150]; Gagne(2005) [151]; LaFleur (2004) [157]; Turner (2002) [154]; Farmer(1999) [155]; Bennett Johnson (1992) [160]	Inaccurate self-reporting can be caused by recall bias, social desirability bias and errors in self-observation.
Paterson (2002) [152]; Hecht (1998) [159]; Bennett Johnson (1992) [160]	The timeframe of the adherence recollection can affect the accuracy of the recall. Specifying the time period can help.
Hawkshead (2007) [150]; Farmer (1999) [155]; Hecht (1998) [159]	Wording of questions, the way a question is asked and the skills of the interviewer can either facilitate or be detrimental to gaining accurate responses.
Turner (2002) [154]; Bennett Johnson (1992) [160]	Being non-judgmental, giving a preamble before adherence questions, and asking about specific behaviours can help validity.

7.3.1 Evidence to recommendations

The GDG considered that self-report is the most widely used method of assessing adherence and that although direct measures of adherence are relevant in some situations they were more interested in making recommendations for routine clinical practice. Indirect methods such as therapeutic effects and prescription ordering and refills are methods which should alert prescribers and dispensers to problems of adherence. In these situations and as part of medicine reviews health care professionals need to be able to discuss medicine-taking with patients. The GDG made recommendations on how professionals should assess adherence using the review of advantages and disadvantages of self-report.

7.3.2 Methods of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies – We included literature reviews and systematic reviews only.

Types of participants - People prescribed medicine for a medical condition.

Duration of studies – No time limit was specified.

Types of interventions - Any interventions intended to change adherence to prescribed medicine which reviews studies which focus on self-report advantages and disadvantages.

Types of outcome measures - No outcome measures specified.

7.3.3 Evidence review

The searches mainly returned literature reviews, rather than systematic reviews, therefore details (of the various studies mentioned in these reviews) were not always given and some only mentioned the studies briefly.

Garber (2004) [162] produced a systematic review on the concordance of self-report with other measures of medicine adherence. They searched a number of databases and identified 2757 articles. The inclusion criteria included studies where at least 2 adherence measures were used, one of which was a self-report measure, the other a non self-report measure. The self-report measures included questionnaires, diaries or interviews and were categorised under these. They found 86 unique comparisons, mostly interviews (57%), questionnaires (27%) and diaries (17%). The non-self-report measures were electronic measures (35%), pill count or canister weight (26%), a plasma drug concentration (20%) a claims-based measure (13%) and a clinical opinion (6%). 43% of the pairings of self-report and nonself-report measures were highly concordant.

Concordance levels were categorised by the following: Kappa results (for categorical variables) over 0.6 were high, 0.6 to 0.4 were moderate and below 0.4 were low. Pearson correlation co-efficient (for continuous variables) over 0.8 were high, 0.8 to 0.4 were moderate and below 0.4 were low. When sensitivity and specificity of the measure was given the measure was as a likelihood ratio (LR). A positive LR greater than 10 was categorised as high, a LR+ of 3 to 10 was moderate and LR+ below 3 was low. If there was no statistical analysis given the authors used an algorithm to categorise.

In the majority (45/59) of those which were not highly concordant, the self-report measure showed higher adherence compared to the nonself-report measure, but this varied widely depending on type of self-report measure. 31% of the interviews were highly concordant with nonself-report measures. Diaries (71%) and questionnaires (55%) were much more likely to be highly concordant with non self-report measures. The difference in concordance by the type of self-report measure was significant (chi-square=8.47, p=0.01). It also depended on the non-self-report measures. Self-reporting had higher concordance with other types of non self-report measures (58%) than electronic measures (17%) (chi-square 14.3, p<0.01). Interviews showed the least concordance with electronic measures, where none of the 15 comparisons were highly concordant. The authors noted that this was a

comparison between measures which could not fully evaluate the accuracy of any of the measures.

The authors concluded that questionnaire and diary methods were preferable over interviewing for measuring adherence. They note that many of the studies did not explicitly compare adherence measures statistically and those that did used simplistic analyses. They also note that the categorisation of concordance was based on arbitrary cut-off points, so different cut-off points could change the levels of concordance between methods.

In summary, questionnaires and diaries were more concordant with other measures.

George (2007) [161] conducted a literature review to assess adherence of COPD patients with disease management programs. They searched OVID and International Pharmaceutical Abstracts. They did not report the inclusion/exclusion criteria or how many studies were retrieved. The adherence measures that were included in the review were self report, inhaler weights, electronic monitoring, inhalation technique assessment, medicine/pill count, pharmacy refill data/claims data and biological assays.

They found that self-reporting of missed doses (by questionnaire) underestimated nonadherence compared to more objective measures e.g. capsule count (Dompeling, 1992), inhaler weights (Rand, 1995) and electronic monitoring (Rand, 1992; Braunstein, 1996; Simmons, 2000). Self-report was shown to have moderate reliability (25% to 67%) compared to objective measures such as canister weight (Rand, 1995) and electronic monitoring (Gong, 1988; Nides, 1993; Bosley, 1995).

Self-reporting of nonadherence of medicine for COPD has shown satisfactory reliability, when compared to objective measures (Dolce, 1991; Nides, 1993; Rand, 1995). Self-report is commonly criticised for overestimating adherence and poor reliability yet those who report nonadherence are likely to be telling the truth (Haynes, 1980; Inui, 1981; Choo, 1999; Erickson, 2001).

The author's concluded that even though electronic monitoring is regarded as the gold standard it is more suited to a clinical trial setting. Self-reporting is the cheapest, simplest and easiest method to assess adherence. Self-report can identify the reasons for nonadherence and therefore the issues can be addressed.

Hawkshead (2007) [150] presented a narrative review of the advantages and limitations of methods for measuring adherence in hypertensive patients. No mention is given to how they searched for these studies or decided to include/exclude. The types of adherence measures were self-report, electronic monitoring, pill counts, pharmacy refill rates, bioassays/biomarkers and direct observation.

They state that self reporting is the simplest method for assessing medicine adherence and can include patient diaries, interviews during office visits and adherence-specific questionnaires. 'Several multi-item questionnaires have been developed and tested in outpatient settings with the explicit aim of ascertaining valid and reliable estimates of adherence to antihypertensive medicines', of which many have reported high measures of validity and reliability (Morisky, 1986; Kim, 2000; Shea, 1992; Krousel-Wood, 2005; Hyre, 2007). There are three previously validated self-reported medicine adherence instruments – the Medication Adherence Survey (MAS), the Brief Medication Questionnaire (BMQ) and the Medical Outcomes Study (MOS). Cook (2005) compared the level of agreement between these and pharmacy refill rates and found correlations between of 0.23, 0.26 and 0.21 between the refill rates and the MAS, MOS and BMQ respectively.

Validated self-report measures can feasibly be used in clinical settings and help to identify those who are nonadherent, and intervene to increase this (Harmon, 2006). The advantages stated are that self-report is simple and economical; it can also gather social, situational, and behavioural factors which can impact on adherence. The disadvantages are the possibility that there could be recall bias, over-estimation of compliance and responses which are socially acceptable. Validity can also depend on the skills of the

interviewer as well as the question construction and timeframe (Farmer, 1999 and Wang, 2004). It is suggested that self-report could be combined with objective information, e.g. prescription-fill data, to improve adherence measurement.

The authors' concluded that selecting the type of measure for clinical practice depends on the intended use of the information, the resources available, patient acceptance and the convenience of the method. A combination of methods may be best to give an accurate assessment of adherence and should be tailored to individual needs.

In summary, some self-reporting questionnaires have been validated and can be simple and feasible to use in clinical settings and identify non-adherers. However they can have biases and overestimate adherence.

Gagne (2005) [151] reported on how to improve self-report measures for nonadherence to HIV medicines, with particular attention to techniques that can be applied with questionnaires administered in clinical practice. Questionnaires are inexpensive and convenient and can be conducted in clinical and research settings, but can vary in terms of accuracy. According to many authors, forgetfulness (Brooks, 1994; Hayes & DiMatteo, 1987; Holzemer, 1999; Rand, 2000; Svarstad, 1999) and social desirability (Felkey, 1995; Gordis, 1969; Gray, 1998; Rand, 2000; Svarstad, 1999) are main factors leading to inaccurate self-reporting of nonadherence. Social desirable answers can depends on how much the patient perceives the desirability of the behaviour to be. Those behaviours perceived as undesirable are under-reported and behaviours perceived as desirable can be over-reported (Cannell 1979; Fowler, 1995). There are techniques suggested for minimising forgetfulness and social desirability (Cannell, 1979; Fowler, 1995; Sudman & Bradburn, 1974; Sudman & Bradburn, 1982) although methods to reduce these are not well-documented, are often derived from clinical practice than controlled experimental studies and their reported effectiveness is inconsistent.

Suggestions were made to reduce socially desirable answers:

- Assuring confidentiality and that information will not be available to HCPs (Eldred, 1998; Gordillo, 1999).

- Explaining that there are no right or wrong answers (Des Jarlais, 1999; Chesney, 1990).

- How the question is asked (Ickovics, in Eldred, 1998; Chesney, 1999; Svarstad, 1999).

- Wording the question to increase the likelihood of gaining certain desired answers, such as nonadherence (loading the question) (Sudman, 1982; Bradburn, 1982; Allaire, 1988).

- Open-ended questions can avoid the pitfalls of response categories (Schwarz, 1985; Sudman, 1982).

Open-ended questions have been used in studies of HIV (e.g. Chesney, 1990) and for measuring adherence/nonadherence (e.g. Svarstad, 1999). Open-ended answers have shown to be less affected by social desirability than close-ended answers (Sudman, 1974). Sudman (1974) also found that open-ended questions were less affected by forgetfulness and recall errors.

Recall can be aided by:

- Item wording, using familiar words and words that have only one meaning and one idea (Sudman, 1982);

- Words should not have blame implications (Averitt, in Eldred, 1998).

- Aided-recall techniques such as memory cues may be useful (Sudman, 1982).

- Specifying a reference time period, especially a recent and short time frame can aid forgetfulness (Brooks, 1994; Chesney, 1999; Holzemer, 1999; Sudman, 1982).

However there is the problem of the time period being too short and not accurately representing the adherence level, as adherence varies over time (Chesney, 1997b; Gray, 1998; Kastrissios, 1998). This could be solved by using a short period of time and administering the questionnaire a number of times over the period. However, this could lead to less motivation and could be costly. Shorter periods of reference could be used when administering the questionnaire only once. According to episodic and semantic memory it may be best to ask more precise information about the past few days and less specific information from a longer time period.

The author concluded that most of the HIV literature used multiple measures of adherence. Adherence to HIV measures could be enhanced by improving self-report measures of nonadherence. Questionnaire designs may have surprisingly beneficial results.

In summary, self-reporting by questionnaire can have biases such as social desirable responses and recall bias. These biases can be minimised using certain techniques.

LaFleur (2004) [157] conducted a brief narrative review of methods to measure compliance with medicine regimens. No search or inclusion/exclusion criteria were given. They state that self-report is the most popular method for assessing compliance as it is inexpensive but is often unreliable (Myers, 1998). Self-report can include patient interviews or self-report surveys. When compared to objective measures e.g. electronic monitoring devices or medicine level monitoring of compliance self-reporting has shown to over-report compliance over 50% of the time (Spector, 1986; Gordis, 1969; Waterhouse, 1993; Straka, 1997). It is also often inaccurate for those reporting non-compliance with medicine-taking. In Kwon (2003) a comparison of self-reporting of antidepressant use with prescription claims showed a 20% difference in those reporting nonadherence to antidepressants. The reasons for any discrepancies with other measures could be that patients do not understand regimens, do not know indications for their medicine, or do not

report behaviours perceived as not socially-acceptable, or forgetting of non-compliance. No references were given for these assertions.

In summary, self-report by interviews or surveys can be inexpensive but can be unreliable and over-report compliance. Those who report non-compliance can also be inaccurate. There could be biases such as social desirability, recall and not understanding medicine regimes.

Turner (2002) [154] reviewed literature, to compare various measures of adherence to antiretroviral therapy. This was a narrative review with no details of search/inclusion criteria. The types of adherence measures in the review were self-report, health care provider estimation, pill counts, pharmacy-based measures, electronic monitors and biological/laboratory markers. They state that self-reports are less complex but that there can be problems with recall over long time periods. Many studies use self-report over the past 4 days but additional questions may be needed, e.g. about weekends, as this tends to be a difficult time for adherence.

All types of self-reporting overestimate adherence compared to other measures (Arnsten, 2001; Golin, 1999; Melbourne, 1999). Even those who report missing doses tend to overestimate adherence compared to other measures (Wagner, 2000). Social desirability biases can also contribute. Those who report problems with adherence usually have poorer adherence with other measures (Haynes, 1980). Those who report nonadherence appear responsive to interventions, and are important to identify (Haynes, 1980).

The validity can be increased with a preamble before the questions about adherence in order to reassure patients that information will not be held against them and that nonadherence is common. Audio computer-assisted self-interviewing is suggested for more sensitive topics (Metzger, 2000; Gribble, 2000).

A study by Bangsberg (2000) compared adherence measured by self-report (by patient interview) with provider estimation and unannounced pill counts. A comparison of pill counts with estimates of and patient self-reporting of

medicines adherence showed that the physician estimates explained 26% of the variation of pill count adherence, and patients' estimates explained 72%. They found that the sensitivity and specificity of estimates of nonadherence (<80% of pills taken according to pill count) were 72% and 95% respectively for patient interview but only 40% and 85% respectively for provider estimates.

They conclude that self-report is more easily obtained but has relatively poor sensitivity but good specificity. However electronic measures have better sensitivity but poorer specificity.

In summary, all types of self-report overestimate adherence, even with those who report nonadherence and biases such as social desirability can occur. Certain techniques could be used to minimise these biases.

Paterson (2002) [152] conducted a brief narrative review to ascertain how adherence to antiretroviral medicine should be measured. The methods reported were electronic monitoring, pill counts, pill recognition, review of pharmacy records, patient self-report, biological parameters, and medicine monitoring and provider prediction of adherence. They noted that how a question is asked can influence self-report of adherence (i.e. in face-to face inquiry or patient-completed questionnaires). A non-judgemental stance can help and this can be achieved by a preamble before the questions to show that they are not being judged and are looking for honest answers (Turner, 2001).

Another disadvantage of self-report (face-to-face interview) is that periods shorter than 7 days are not long enough to determine the percentage of adherence likely, however some patients may not correctly report adherence for 7 day periods. They state that additional questions may be necessary to counteract this e.g. about adherence at the weekend.

One method to counteract the problems of gaining honest answers is computer-assisted self-interviewing (Bangsberg, 2001) or diary. Diaries hold

an advantage as they can be inexpensive and accurate. Their disadvantage is that some may complete them retrospectively or not at all.

Paterson (2002) asserts that self-report is 'likely to be the simplest means of assessing adherence' and so the reliability is important to assess. Adherence was found to be 'considerably higher' than that measured by electronic monitoring or pill count (Liu, 2001). Self-report overestimates adherence. It is most useful in those who admit to being poor adherers (Murri, 2000). They conclude that electronic monitoring devices are the closest to a gold standard in adherence measurement.

The authors conclude that there is no gold standard for measuring adherence and that electronic monitoring, in their opinion, may be the closest, yet it has some limitations. If a patient is failing to respond to treatment, self-report or pill identification should be the first option. If they report adherence this could be confirmed by electronic monitoring.

In summary, various self-reporting measures were reported. Interviews may be too late for accurate recall or may be too early to gain useful adherence information. Diaries are inexpensive and can be more accurate as there is no recall bias, however they may not be completed or completed retrospectively. Self-report can overestimate adherence but can identify those who report nonadherence.

Miller (2000) [153] reviewed current literature of measures of adherence of antiretroviral medicines in clinical trials. The types of measures of adherence were self-report, clinician estimates, pill counts, pharmacy records, clinic attendance, plasma levels, surrogate/indirect laboratory markers and electronic monitors. They report that the simplest method of measuring adherence is self-report. But there is no standardised instrument. Self-reported surveys are quick and avoid sophisticated methodology or equipment and are inexpensive compared to other methods of measurement. They have limitations, such as significantly exceeding adherence measured by other objective methods (Bond, 1991; Stratka, 1997; Cramer, 1991). HIV studies confirm this (Golin, 1999; Arnsten, 2000; Paterson, 1999; Bangsberg,

1999). Interviews and surveys often promote socially acceptable responses (DiMatteo, 1982). Less adherent patients report higher adherence than they actually had (Bond, 1991). Memory can also affect the accuracy of reporting adherence. Most surveys use broad response categories to report the proportion of pills taken, thus small degrees of nonadherence is hard to distinguish with self-report. The information is useful, but accuracy is limited and biased towards higher adherence.

Self-reported nonadherence has been associated with worse virologic outcomes (Demasi, 1999; Bangsberg, 1999; Duong, 1999; Murri, 1999; Le Moing, 1999) and as an independent predictor of clinical response to HAART when controlling objective virologic and immunologic markers (Montaner, 1999). They assert that even though it is an imperfect measure it can provide information that explains variation in clinical response to antiretroviral therapy which is not explained by other clinical factors.

The authors concluded that each method of adherence measurement has its own strengths and weaknesses. Caution should be taken when extrapolating adherence measured in clinical trials into clinical practice. Many measures have been independent predictors of clinical outcome. They may identify slightly different nonadherent populations. The different measures may complement each other and they would recommend using more than one measure, where possible.

In summary, self-report surveys are simple and inexpensive but can overestimate adherence. Interviews and surveys can have social desirability and recall biases. Also as categories are large, small degrees of nonadherence are hard to detect. There is no standardised instrument. However it can explain variation in clinical responses to ART.

Farmer (1999) [155] conducted a review of methods for measuring and monitoring medicine regimen adherence in clinical trials and clinical practice. They searched Medline for the years 1990 to 1999 and retrieved 2630 articles regarding patient compliance. The types of adherence measures included were self-report, biomarkers, direct patient observation, pill counts,

prescription record review (manual and electronic) and electronic monitoring. Types of self-report included questioning/interrogation and the use of diaries and survey instruments. They tabulated the various methods for assessing adherence and their advantages and disadvantages. Patient interviews are easy to use and inexpensive but the patient can be influenced by question construction and interviewer's skill. Adherence questionnaires are easy to administer (on site, mail, telephone), can be validated and may explain patient behaviour. However there is a lack of continuous data and the accuracy is instrument-dependent.

Patient interviews are generally considered the most unreliable for assessing adherence (Grymonpre, 1998; Matsui, 1994; Craig, 1985; Straka, 1997; Park, 1964; Inui, 1981; Gordis, 1969). Those who report nonadherence are usually correct, whereas those who say they are adherent may not be (Cramer, 1991). However it can depend on the method used and how it is used. Assessing self-reporting is difficult mainly because there are so many methods. The interviewer's skill and the construction of the questions can affect the accuracy and validity of self-report. The relationship and communication between the HCP and patient can statistically significantly affect compliance (Davis, 1969). Highest compliance was found with those who joked, laughed and sought suggestions from their GP. The wording of questions can affect the response, and implications of blame can encourage biased responses (Ross, 1991). Some answers are socially desirable and concealed their real behaviour (Sherbourne, 1992). It is hard to assess studies of interviews as the way they are asked could bias the result.

Stewart (1987) looked at 2 compliance questions in an interview to assess medicine-taking behaviour. Comparing the results to pill counts, the questions had a specificity of 69.8% and sensitivity of 80%, therefore an overall 74.5% accuracy. The time frame used for recall can differ, some researchers do not specify, others are 7-10 days and some are a month (Grymonpre, 1998; Dirks, 1982; Straka, 1997). To correct these problems some researchers have tried to construct a standardised questionnaire for measuring adherence. For example Morisky (1986) developed a 4-item questionnaire specific to

medicine regimen adherence. It was assessed on unidimensionality, reliability and concurrent validity with blood pressure control. The instrument's sensitivity was 81% and specificity 44%. It was not found to be efficient at predicting poor adherence (Morisky, 1986).

Svarstad (in press at time of review) developed a self-administered instrument called the Brief Medication Questionnaire. The accuracy was assessed using MEMS. There were 3 sets of questions – 5 regimen screen items, 2 belief screen items and 2 recall screen items. The sensitivity for repeat nonadherence was 80% for the regimen screen, 100% for the belief screen and 40% for the recall screen. The specificity for repeat adherence had 100% for the regimen, 80% for the belief and 40% for the recall screen. The accuracy of reported repeat nonadherence was 95% for the regimen, 85% for the belief and 40% for the recall screen.

The authors concluded that each method has strengths and weaknesses depending on the intended use. When selecting a specific method an assessment of each method's validity should be undertaken. A combination of methods is recommended.

In summary, several methods of self-report were examined. Interviews are simple and inexpensive, but can depend on the interviewer. Questionnaires can be administered in a variety of methods, but are considered the most unreliable. Those who say they are nonadherent are usually being truthful but many who say they are adherent may not be.

Bender (1997) [156] conducted a literature review to assess nonadherence in asthmatic patients. A search of Medline was made from 1990 to 1997 of all pertinent articles, preferably controlled studies. Types of adherence measures were biochemical measurement, clinical judgement, medicine measurement, pharmacy database review and electronic medicine monitoring. Self-report measures can be collected by interview, diaries and questionnaires but no validated adherence-specific questionnaire is commonly used as they are often specific to the studies. Self-report measures are simple, inexpensive and usually brief and so they are commonly used to measure adherence.

Especially in the clinical setting they are the best measure for collecting information on beliefs, attitudes and experiences with medicine regimes. Accuracy with other measures is highly variable. Spector (1986), Coutts (1992) and Gibson (1995) compared asthmatics self-reporting of inhaler usage with electronic medicine monitoring devices and they showed that asthma diaries usually overestimate adherence. Demands of the setting can influence the usefulness and reliability of the information gained from self-reporting. These can be a desire to please on the part of the patient and the Health Care Professional's skill and sensitivity in eliciting self-reports. When collected well it can give good insight into patients' problems with adherence. As they are unlikely to identify themselves as non-adherers unless they are this helps identify them (Coutts, 1992; Spector, 1986; Dolce, 1991; Morisky, 1990).

The authors state that while self-report may not be a sufficient measure of adherence in many settings and particularly in research, it is probably a necessary measure in all settings.

In summary, self-report measures are simple, inexpensive, brief and the best way of collecting information in the clinical setting. However diaries overestimate adherence and the demands of the setting can influence the usefulness and reliability of the measure.

Rand (1994) [158] reported in a narrative review on measuring adherence to asthma medicine regimens. They did not state search or inclusion criteria. The types of adherence measures included in the review were biochemical measures, observation of MDI technique, clinical judgement, medicine measurement and medicine monitors.

They state that self-report is the most inexpensive and quick way of measuring adherence (Soutter, 1974). The possible advantage of diary cards is that they can measure adherence across time and can reveal patterns between the disease exacerbation and compliance with the medicine. As there are many medicines used within asthma prescribing, it can help to see the adherence of certain medicines rather than just overall. It can also

specifically assess overuse, inappropriate use or erratic use of medicines as well as triggering events for the need for medicine e.g. in Kesten (1991). Asthma diaries may share commonalities but there is no standardised diary as such in research. A disadvantage of asthma diaries is they may be be complex and time-consuming. Also criteria of acceptable adherence may differ from patient to patient. One way to evaluate the level of adherence is to use trained, masked, medical personnel to score the compliance. It is preferable to develop standardised compliance criteria for all raters and train them by a standardised protocol and make sure there is inter-rater reliability.

Many studies have used questionnaires to collect clinic or follow-up data for patient adherence (Bailey, 1987; Kinsman, 1980; Dolce, 1991), mainly designed for a particular research project. Many include adherence questions within a larger questionnaire, such as the 76-item Revised Asthma Problem Behaviour Checklist (RAPBC) and the 72-item Asthma Problem Behaviour Checklist (APBC). These have been found to be reliable with test-retest correlation coefficients of r=0.95 and r=0.80 respectively. However no reliability and validity information was available for those items specifically measuring adherence to medicine.

Rand (1994) points out that both asthma diaries and self-report are the most common methods for assessing asthma medicine adherence but these instruments, because they are not standardised or not published, rarely have their validity and reliability assessed. Except for Adherence Scale and Inhaler Adherence Scale (Kinsman, 1980; Dolce, 1991; Bailey, 1990), which are six-item scales based on Morisky's work (1990). This instrument was found to have a Chronbach's alpha of 0.76 and 0.69 and was concordant with outcome measures in the UAB adult asthma study.

The limitations of self-report have been mentioned by many authors (Masur, 1981; Mawhinney, 1991; Cramer, 1989; Rand, 1992). When compared to objective measures it varies highly on the degree of accuracy (Gordis, 1966; Mattar, 1974). Diary self-reports were compared to an electronic medicine monitoring device to measure adherence to asthmatic medicine by Spector

(1986). The findings were that all patients self-reported using the inhaler on certain days, whereas the measured medicine suggested just over half (52.6%) actually did so. Adding a diary can add more complexity to the patient regime than there all ready is. It has been shown that the greater the complexity of a regime the lower the compliance (Masur, 1981). Some participants alter their records of medicine use to appear compliant (Mawhinney, 1991; Rand, 1992). This can be improved if they also have reporting by the family/partner of the patient (Paulson, 1977).

Self-reporting can also depend on the individual patient or practitioner. For example elderly patients may have memory impairment, especially when taking many medicines and therefore do not report accurately. Long-term usage may be forgotten but they may be able to recall recent usage. The skill and sensitivity of the Health Care Practitioner can also play a role in how much information is given and the reliability of it. When collected carefully it could be very good insight into the problems of a patient's adherence. Also it is unlikely that patients will represent themselves as non-adherers (Gordis, 1976) so it will identify non-adherers correctly.

In summary, self-report is generally inexpensive and quick. Diaries can measure adherence across time and reveal any patterns and overuse of medicine. However there is no standardised diary and it can sometimes be complex and time consuming. If there is no standardised questionnaire or diary then no validity or reliability are assessed. Therefore there is variation in accuracy and it can depend on the individual or practitioner.

Bennett-Johnson (1992) [160] conducted a narrative literature review of adherence measurement in diabetes management. No search or inclusion criteria were given. The types of adherence measures used were health-status indicators, health provider ratings, behavioural observations and pill counts.

They point out that self-report of regimen adherence is often mistrusted. Patients may say one thing but do something completely different, often because of what they think the professional wants to hear. However

noncompliance self-reporting appears more valid than self-reporting of compliance (Diehl, 1987). Asking about specific behaviours can lead to better adherence data (Cerkoney, 1980; Cox, 1984; Shlenk, 1984; Brownlee-Duffeck, 1987; Hanson, 1987; Hanson, 1988; Hanson, 1990). There have only been a few that have looked at the reliability of these reports (Hanson, 1987 and Hanson, 1988). If asked to report their specific behaviours over a certain time period, the data can be good quality (Glasgow, 1987; Johnson 1986). Glasgow (1987) used written diaries successfully to measure adherence and Johnson (1986) adapted the 24-hour recall interview (which is a standard dietary assessment method) to use as a general adherence assessment strategy with IDDM patients. The authors state that 'in a series of studies the authors have demonstrated both the reliability and validity of this technique' (Bennett Johnson, 1992). These studies referred to are Johnson (1986); Johnson (1990); Spevack (1991); Reynolds (1990); Johnson (1990) and Freund (1991). Multiple interviews are recommended to ensure representation of adherence behaviours.

One disadvantage with self-reporting is problems of memory recall. Where possible a significant other should additionally be interviewed regarding the patient's behaviour.

The advantages of self-report are numerous, as reliable information can be obtained; interviews can be done over the telephone making them accessible; the patient does not have to do very much apart from give their time for an interview. They however do need trained interviewers, or with multiple interviews and multiple patients the process can take a lot of time and effort. No references were made for these assertions.

In summary, self-reporting of non-compliance is likely to be more valid, whereas compliance reporting is not valid. They can ask about specific behaviours and find out about what leads to non-compliance. It is easy for the patients to do and interviews can be done by telephone call. However there are biases with recall and people may say one thing but do another and there can be errors in reporting e.g. self-observation skills.

Dunbar (1989) [163] reviewed the methods to assess adherence to arthritis medicine with a review that included '16 representative studies of compliance'. No inclusion/exclusion criteria or search details were given. The review included self-report, clinician judgement, therapeutic outcome, direct observation, biological measures, pill counts, pharmacy refills and electronic monitors.

They noted that a major problem is the accuracy of reporting, with poor compliance usually underreported. One issue is the memory decay when assessing adherence (Farr, 1987). Effects, such as not realising the diminishment of higher adherence levels has occurred and moving past events forward in perception can all lead to inaccuracy. Motivational factors are also important, errors in reporting can be due to self-observation skills, especially when the compliance behaviour is itself variable. Misconceptions of the regimen may lead to errors through inaccurately labelling events compliant or noncompliant.

Self report has advantages in that it can identify some noncompliance in a cost-efficient manner and permits an in-depth study of the types of errors that patients can make which leads to non-compliance. It also has been shown to have reasonable sensitivity and specificity in discriminating those who comply from those who do not. In one study of medicine adherence self-report showed 100% sensitivity and 40% specificity when serum levels were used as a standard (Craig, 1985). The authors assert that 'self-report can be a useful measure. However, it is important to attend to the collection of accurate information.'

The authors conclude that self-report can be a useful measure and interviewers' skills are very important. Clinical measures are fraught with problems and there is no perfect measure.

In summary, self-reporting can mean poor compliance is underreported, there can be recall bias and self-observation skills may be erroneous. It is cost-efficient and can identify non-compliers.

Hecht (1998) [159] reported briefly with a narrative review on measures for HIV adherence in clinical practice. The types of adherence measures mentioned were self-reporting, medicine levels, physician judgement, MEMS, pill counts and prescription refills.

Sackett (1975) compared self-report to pill counts. Of those that reported having less than 80% adherence, 95% were found nonadherent by pill count. Those reporting that they were adherent over 80% of the time, were shown to be nonadherent by pill count 34% of the time. Gilbert and Sackett's studies, suggest that self-report is more accurate than physician assessment. Thus if HCPs want to know if patients are taking anti-retroviral therapy, they need to ask them rather than relying on their judgement. When they say they are missing medicine, believe them, as this is mostly the truth. Patient self-report tends to overestimate adherence. Those who report missing doses infrequently may have a significant problem of nonadherence.

Hecht (1998) says that what matters is how Health Care Practitioners ask the questions. Stating it should be in a specific, non-judgmental way and one that allows them to disclose nonadherence. Therefore, questions should not imply that they are wrong if they do not take their medicine the way they are 'supposed to'. A time period must also be specified. No references given for these conjectures. Measuring medicine levels should be regarded as a supplementary measure. Electronic pill monitoring, pill counts, reviewing prescription refills can be useful adjuncts to self-report in certain contexts, but every method has its limitations.

In summary, self-report is more accurate than Health Care Practitioners' judgement alone. It tends to overestimate adherence. It depends on how the questions are asked and a time period must be specified.

Overall summary

This evidence review focused on the advantages and disadvantages of self-report for assessing adherence. These were primarily narrative reviews rather than systematic reviews.

These reviews reported that all measures of adherence have strengths and weaknesses. There is no gold standard. Self-report can vary in reliability, yet it was thought generally to be a useful measure of adherence. Those who report nonadherence are likely to be telling the truth. It is also good for finding out the reasons for nonadherence. In a couple of studies it was suggested that self-report could be the first measure of adherence and for those who report adherence it could be supplemented by other measures. It is primarily a clinical tool, whereas other measures may be more relevant to clinical trials.

Any questionnaire which measures self-report should be well-designed and validated. Many of the reviews reported that the success of interviews as a measure largely depended on the skills and communication of the interviewer. It could depend on the way a question is asked.

8 Interventions to increase adherence to prescribed medicine.

8.1 Recommendations

[Hyperlink to recommendations section Interventions to Increase Adherence](#)

8.2 Introduction

Adherence is defined as 'the extent to which the patient's behaviour matches agreed recommendations from the prescriber' [1]. Adherence describes patient behaviour in the actual taking of medicines. This definition of adherence presumes that the patient has reached some agreement with the health care professional about the prescribed medicine. The Guideline Development Group was interested in interventions that would support patients in taking medicines following agreement with the health professional.

Nonadherence can be intentional or unintentional. Nonadherence is unintentional if the patient does not take the medicine, for example, due to forgetfulness or not being able to access the medicine because of problems with packaging and dexterity. Nonadherence is intentional when the patient makes a decision to not take the medicine as previously agreed or to take it in a way other than recommended by the prescriber because of their own beliefs and appraisals of the medicine and medicine-taking. Both intentional and unintentional nonadherence can occur regarding the amount or duration of missed medicine e.g. a single dose may be missed, a patient may miss several days of medicine or a patient may permanently stop taking medicine. In some patients nonadherence takes the form of the patient reducing or increasing the dose of prescribed medicine rather than omitting it.

8.3 Methods

The aim of the evidence review is to identify the most relevant, published evidence to answer the key clinical questions generated by the GDG. Reviews of the evidence using systematic methods relating to searching and

appraisal were conducted to answer the clinical questions in line with the NICE Technical Manual. The GDG and project teams agreed appropriate inclusion and exclusion criteria for each topic area in accordance with the scope. Additional evidence reviews were developed as an update to the 2005 Cochrane review[7] titled: "interventions for enhancing medicine adherence". The Haynes review aimed to summarise the results of randomised controlled trials (RCTs) of interventions to help patients follow prescriptions for medicines for medical problems, including mental disorders but not addictions. The review was organised by disease except for short-term treatments where not enough studies were retrieved on any individual disease condition to allow grouping by disease.

The main results of the Cochrane review were: For short-term treatments, four out of nine interventions (reported in eight RCTs) showed an effect on both adherence and at least one clinical outcome, while one intervention reported in one RCT significantly improved patient compliance, but did not enhance the clinical outcome. For short-term treatments, the main characteristics of the interventions were:

- counselling patients about importance of adherence, reinforced with written instructions.
- counselling from a hospital pharmacist and a follow-up phone call compared to a standard advice sheet and referral to a family physician that prescribed the same medication.
- comparing pre-packed chloroquine tablets versus chloroquine syrup.
- comparing dispensing azithromycin for infections free in the emergency department with a prescription that could be filled for free at a pharmacy.
- comparing nasal spray with varying levels of training and instructions.

For long-term treatments, 26 out of 58 interventions reported in 49 RCTs were associated with improvements in adherence, but only 18 interventions led to improvement in at least one treatment outcome. Almost all of the interventions that were effective for long-term care were complex, including combinations of

---

[7] first published in 2002

more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, psychological therapy, crisis intervention, manual telephone follow-up, and supportive care. Even the most effective interventions did not lead to large improvements in adherence and treatment outcomes. Six studies showed that telling patients about adverse effects of treatment did not affect their adherence.

These results led the authors to conclude that for short-term treatments several quite simple interventions increased adherence and improved patient outcomes. Current methods of improving adherence for chronic health problems are mostly complex and not very effective, so that the full benefits of treatment cannot be realised and that further research concerning innovations to assist patients to follow medicine prescriptions for long-term medical disorders is required.

A more recent version of this Cochrane review has now been published in 2008. The main results were: for short-term treatments, four out of ten interventions reported in nine RCTs showed an effect on both adherence and at least one clinical outcome, while one intervention reported in one RCT significantly improved patient adherence, but did not enhance the clinical outcome.

For short-term treatments, the main characteristics of the interventions were:

- counselling patients about importance of adherence, reinforced with written instructions.
- counselling from a hospital pharmacist and a follow-up phone call compared to a standard advice sheet and referral to a family physician that prescribed the same medication.
- comparing pre-packed chloroquine tablets versus chloroquine syrup.
- comparing dispensing azithromycin for infections free in the emergency department with a prescription that could be filled for free at a pharmacy.
- comparing nasal spray with varying levels of training and instructions.

For long-term treatments, 36 out of 81 interventions reported in 69 RCTs were associated with improvements in adherence, but only 25 interventions led to improvement in at least one treatment outcome. Almost all of the interventions that were effective for long-term care were complex, including combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, psychological therapy, crisis intervention, manual telephone follow-up, and supportive care. Even the most effective interventions did not lead to large improvements in adherence and treatment outcomes. In this update the authors also reported that for short-term treatments where several quite simple interventions increased adherence and improved patient outcomes the challenge is that there are inconsistent results from study to study with less than half of studies showing benefits.

The evidence in the Cochrane review was organised by disease, however as this guideline is intended to be a generic document we re-arranged the evidence according to the type of intervention. We also conducted additional specific searches for several questions. This is described below.

The titles and abstracts of studies retrieved by electronic searches were scanned for relevance to the topic on interventions to increase adherence. Any potentially relevant publications were obtained in full text. These were then reviewed to identify the most appropriate evidence and were then allocated to the relevant key clinical questions. Following this, the assessment of study quality; synthesis of the results; and grading of the evidence was undertaken.

While the GDG were interested in any intervention that might be useful in supporting adherence, the key clinical questions agreed by the GDG included questions on a number of specific interventions. We initially conducted one broad search in order to find evidence on interventions to increase adherence. This search allowed us to pick up any intervention designed to increase adherence and then allocate the evidence to the respective clinical question. This reduced the duplication of sifting and reviewing of the evidence. This search was supplemented by specific searches in areas considered important

by the GDG where we also included some observational studies. These were areas where the broad search left considerable uncertainty but the interventions were considered either potentially important in clinical practice or areas where popular preconceptions may exist.

These were:

- Does change in dosing regime affect adherence to prescribed medicine?
- Does drug formulation/packaging affect adherence to prescribed medicine?
- Do prescription charges affect adherence to prescribed medicine?
- Does the use of multi-compartment medicine systems increase adherence to prescribed medicine?
- Do medicine reviews affect adherence to prescribed medicine?

8.4 Evidence to recommendations : difficulties in interpreting studies on interventions to improve adherence

Given the advances of medical therapies and the increase in prescribing and medicine use in the last decades, it could be expected that this has been accompanied by a greater understanding of the processes of adherence and nonadherence and the effectiveness of interventions to promote adherence. In general however the current body of literature on adherence is of poor methodological quality and was considered inadequate to answer many of the GDG questions on interventions to increase adherence. Medicine-taking does not appear to be recognised by many researchers as a complex human behaviour which should be studied using complex interventions in line with the MRC framework (2000) [164]. The GDG considered that the difficulties with studies on interventions to increase adherence were common across studies.

The issues affecting quality of the studies appraised for interventions to promote adherence are outlined below:

(a) The content and method of delivery of the components of the intervention are not well described and differ in different studies.

(b)The lack of distinction between content of intervention and how it was delivered makes it impossible to understand the overall poor and contradictory outcomes.

(c)The majority of the studies do not assess a single intervention but include multi-component interventions. In a trial the two interventions being compared may each have a different set of components. This means it is not possible to compare one trial with another and even when an intervention works it is not possible to know which component or combination of components is effective.

(d) Studies do not report whether the planned interventions took place as intended in the study protocol.

(e) No standard method of assessing adherence is used.

(f) There is infrequent justification of the relevance of certain interventions in improving adherence e.g. there is no theoretical framework informing the studies and this precludes development of understanding of phenomena of adherence/nonadherence.

(h) Studies had frequently small sample sizes and inadequate description of settings and existing rates of adherence; generalising of these interventions to routine clinical practice is therefore not possible.

(i) Many of the interventions are extremely complex and labour-intensive and are carried out by paid research staff and thus it is unknown whether they could be carried out in a non-research setting.

(i) Within the long-term conditions, even the most effective interventions did not lead to substantial improvements in adherence and treatment outcomes.

(k) Interventions are not targeted to causes of nonadherence – it is likely therefore that some interventions may be more effective than evidence suggests if directed to actual cause of non–adherence in individual patients.

(l) Comment is not made on patient involvement in decision to prescribe medicines.

(m) Few studies mention whether raters of outcome or adherence were blind to whether subjects were in the intervention or control group.

(n) Despite the comprehensive and detailed searching, some trials that met our criteria may have been missed. The literature on patient adherence is not well indexed as it sprawls across the traditional disease areas and as a result of all these, there is little information available to fully understand why one intervention works and other very similar ones did not. Our concern about the evidence in this area is mirrored in other key reviews and trials [3].

(o) The evidence reviews on cost effectiveness of interventions to improve adherence is discussed in chapter 10. The GDG considered these when making recommendations. The GDG noted that interventions to increase adherence may or may not lead to improved clinical outcomes. Increased adherence may result in more adverse effects. Differences in clinical outcomes will depend on the effectiveness of the adherence-enhancing intervention, as well as the dose-response related efficacy of the medicine. Increased adherence was generally associated with increased efficacy but did not have a consistent relationship with costs in the reviews. Assuming the intervention is effective and raises adherence rates, it still remains uncertain what the incremental treatment effect of the medicine will be. The intervention may result in a potential QALY loss due to side effects of the medicine (where before non adherence would have prevented them).

The GDG considered that results of the reviews need to be interpreted with caution, as some of the elements that have worked within some of the trials are present in other studies that have not yielded significant improvements. The GDG were interested in simple interventions that might be targeted to

individuals but the majority of the studies are complex interventions with an extremely wide range of components.

8.5 Does change in dosing regime affect adherence?

Related references	Evidence statements (summary of evidence)
Shi (2007) [165]; Schroeder (2004) [166]; Iskedjian (2002) [167]; Claxton (2001) [168] Baird (1984) [169]; Brown (1997) [170]; Girvin (1999) [171]; Portsmouth 2005 [172]; Molina (2007) [173]	Systematic reviews and RCTs show that simplification of dosing frequency can increase adherence to prescribed medicine.
Schroeder (2004) [166]; Iskedjian (2002) [167]; Portsmouth 2005 [172]; Molina (2007) [173]; Baird (1984) [169]; Girvin (1999) [171]	Two systematic reviews and four RCTs show that reducing twice-daily to once-daily dosing may increase adherence to prescribed medicine.
Claxton (2001) [174]; Rudd (2004) [175]; Parienti (2007) [176]	Evidence from one low quality systematic review and two RCTs showed that once-daily dosing compared to twice-daily did not increase adherence to prescribed medicine.

8.5.1 Evidence to recommendations

For general discussion of limitations of evidence see section 8.3.

The GDG were interested in whether there was evidence to indicate that changes in dosing regime would improve adherence. The findings of the evidence review were that reducing the complexity of a regime can increase adherence but the quality of evidence was low. The evidence from the qualitative interviews indicated that the difficulty for patients is integrating the regime into their lives rather than dose complexity per se and the GDG

recommendation is that changes to dosing regime need to be tailored to needs of individual patients. The GDG considered that the evidence does not support that developing once-daily formulations and combined pills will necessarily improve adherence.

One area of interest for the GDG was the use of medicines by injection particularly antipsychotic medicines and contraceptives. This option could be classified as changes to dose regime or medicine formulation. The GDG were clear that using medicines by injection in this way may be an appropriate choice where patients have non-intentional adherence i.e. they forget to take their medicines. As such this choice should be offered to patients. The GDG were aware of evidence from qualitative synthesis that patients with mental health problems can feel coerced to take medicine and wished it made clear that the aim of our recommendations is to support informed adherence.

8.5.2 Methods of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies – We initially included only randomised controlled trials (RCTs) of interventions to increase adherence. The excluded studies list from the Cochrane review was checked as we have included those studies with less than 80% follow-up of participants. As with the Cochrane review we found only a small number of studies that fulfilled our criteria. For this evidence review we excluded any randomised controlled trials that evaluated changes in dosing regimes but did not assess the same medicine in all comparative groups. The GDG requested a further search to pick up any systematic review published after the Cochrane review search cut-off. However, the included systematic reviews did not follow this criterion.

Types of participants - people prescribed medicine for a medical condition.

Duration of studies - six months follow-up from the time of patient entry for long-term regimens for the RCTs. No time limit specified for short-term conditions.

Types of interventions - any interventions intended to change adherence to prescribed medicine. As the Cochrane review is presented by condition, we have used the evidence extracted in that review and reconfigured it by intervention.

Comparator - a comparison of different dosing regimes, for the same medicine to ensure no confounding of results.

Types of outcome measures – inclusion criteria (as defined in the Cochrane review) were expanded by including studies that used adherence as the only outcome variable as opposed to adherence and treatment outcome variables. The excluded studies list of the Cochrane review was cross-referenced to ensure that no potentially relevant study was missed out.

8.5.3   Evidence review

8.5.3.1   Does change in dosing regime affect adherence?

We found many studies comparing dosing regimes but these were often comparisons of different medicines. It was necessary to only include studies that compared the same medicine so that the results would not be confounded.

Systematic Reviews

One recent review of systematic reviews and empirical studies **(Shi 2007)** [165] looked at the impact of dose frequency on compliance and health outcomes, particularly for injectables. Inclusion criteria were that the studies should compare different dose frequencies, including injectable medicines and be published in a peer reviewed journal. Exclusion criteria were that the article should not focus solely on dosage forms, dose administration or dose timing.

Full text reviews were conducted on a total of 64 empirical studies and 25 literature/systematic reviews. No details were given on overall methodological quality of the studies.

Results were presented through five main areas: cardiovascular diseases, diabetes, nephrology/urology, neurology/psychiatry and rheumatoid/muscle. Of the 21 studies that measured compliance, 17 reported a positive impact (no details of significance given) of reducing dose frequency on compliance, whilst inconclusive results were seen in four. Details of the dose frequency reductions contained in the studies were not provided by the review.

Articles not measuring compliance as the main outcome looked at efficacy and other outcomes of extended-release medicines in comparison to the immediate-release forms. The studies also supported the general benefits of reducing dosing frequency on improved quality of life or patients' satisfaction (6 studies), greater control over side effects (5 studies) and improved economic outcomes using extended-release formulation (2 studies).

Schroeder (2004) [166] used the Cochrane methodology to review dosing regimes and adherence in hypertensive patients. The methodological quality of the primary included studies was assessed to be generally low. Many RCTs showed marked heterogeneity in terms of participants, interventions and outcomes. A pooled analysis was considered inappropriate as results on adherence were reported in many different ways. Simplifying dosing regimens improved adherence in 7 of 9 studies with relative improvement in adherence increasing by 8% to 19.6%. All of the studies that used objective outcome measurement (Medicine Event Monitoring System) showed an improvement in adherence through the use of once-daily instead of twice-daily dosing regimens, although four of these compared two different medicines. Only 1 study showed an increase in adherence (90% vs. 82%; p<0.01) together with a reduction in systolic blood pressure of 6 mm Hg (p<0.01).

A weak meta-analysis conducted by **Iskedjian (2002)** [167], combined comparative studies of different research designs including prospective trials (RCTs and cohort studies), retrospective chart reviews and database

analyses. Adherence was defined differently in various studies and different instruments were used to measure patient adherence. In this meta-analysis, all variables that could affect adherence other than daily dose-frequency were assumed to be equal between comparators.

Eight studies involving a total of 11,465 observations were included (1830 for daily [OD] dosing, 4405 for twice a day dosing [BID] and 4147 for dosing >2 times daily [>BID] and 9655 for multiple daily dose [MDD]). The primary objective was to assess adherence. The average adherence rate for OD dosing (91.4%, s.d=2.2%) was statistically significantly higher than for MDD (83.2%, s.d=3.5%; $p<0.001$). The difference between adherence rates for OD dosing (92.7%) and BID dosing (87.1%) was also statistically significant ($p=0.026$), although the difference in this analysis was smaller than in the OD-versus-MDD analysis (5.7% vs. 8.2%). The difference in adherence rates between BID dosing (90.8%, s.d=4.7%) and >BID dosing (86.3%, s.d=6.7%) was not statistically significant ($p=0.069$). However, a subgroup analysis using a stricter definition of adherence (≥90% intake) did reveal a statistically significant difference between BID and >BID dosing (respective adherence rates of 76.1% and 67.0%, $p<0.001$).

Another systematic review published by **Claxton (2001)** [168] also found that simpler, less frequent dosing regimes resulted in better compliance. This systematic review appeared to include several study designs. This review showed strong methodological limitations particularly in terms of data analysis. The study did not give full details of inclusion/exclusion criteria and thus possibly including studies that compared different dosing regimes in different medicines. The results should therefore be viewed with caution.

Seventy-six studies were included in the review. By combining all data it was found that increasing the number of daily doses was statistically significantly related to a decline in compliance ($p<0.001$ among dose schedules). Comparisons between dose regimens showed that compliance was statistically significantly higher with once daily regimens vs. 3 times daily ($p=0.008$) or 4 times daily regimens ($p<0.001$). Compliance with twice daily

dosing was statistically significantly higher than 4 times daily dosing (p=0.001). There were no statistically significant differences in compliance between once daily and twice daily regimens or between twice daily and 3 times daily.

Randomised controlled trials

Three RCTs **Baird (1984)**♦ [169]; **Brown (1997)** [170] and **Girvin (1999)**♠ [171] from the Cochrane review (2005), assessed the effect of the simplification of a dosing frequency. **Baird (1984)** [169] compared twice a day 100mg Betaloc tablets to once daily 200mg Betaloc Durules, in a sample comprising 389 participants. Mean age of the participants was 52.7 years for the twice daily group, compared to 54.5 years. Over the total study period, compliance exceeded 80% in 96.4% of patients in the Durules group and 90% of patient in the Betaloc tablets group (p=0.0591). When to 90% levels of compliance were compared, overall compliance exceeded this level in 92.8% of patients on Durules and in only 81.5% of patients on tablets (p=0.009). A statistically significant effect in increasing adherence was reported. **Brown (1997)** [170] tested controlled-release niacin twice daily to regular niacin, four times daily, in the treatment of hyperlipidemia and coronary artery disease, in 29 male participants aged ≤65 years. Compliance was 95% with the controlled-release niacin versus 85% with regular niacin (p< 0.001). **Girvin (1999)** [171] tested enalapril 20 mg once daily versus enalapril 10 mg twice daily in the treatment of high blood pressure. Sample size comprised of 27 patients. Mean age of participants was 62 years. Overall medicine adherence was improved with once-a-day dosing. The difference in percentage of doses taken by pill count between the two periods was statistically significantly in favour of the once daily regimen (p<0.01), as was the percentage of doses taken as measured by a pill container that recorded lid openings (MEMS) (p< 0.001).

♦ Study information indicates that duration is less than 6 months, however this is not stated in Cochrane Review.
♠ Study with less than 6 months duration that was included in the Cochrane Review as results for blood pressure outcomes were negative.

One RCT **Portsmouth (2005)** [172] included in the 2008 revision of the Cochrane review assessed whether virologically controlled HIV-1-infected individuals switched from a twice-daily antiretroviral regimen to a once-daily regimen demonstrate improved adherence and quality of life while maintaining virological control. Forty-three patients were included in this study, with 22 in the once daily (intervention) group, and 21 in the twice daily (control) group.

The once-daily group (intervention): the prolonged release capsule group (PRC) were assigned to take d4T PRC/3TC/EFV all once-daily (24 h apart); Twice daily (control group): participants in the control group were assigned to continue either d4T IR/3TC/EFV or Combivirs/EFV as per their screening regimen. Note: participant weighing less than 60 kg were prescribed either 30 mg of d4T IR or 75 mg of d4T PRC.

After randomisation, patients allocated to the PRC (intervention) maintained this high adherence, while those allocated to IR (control) showed a statistically significantly reduced adherence in 'taking compliance' (p=0.0237) (percentage of prescribed number of doses taken), 'correct dosing compliance' (p=0.0104) (percentage of days with correct number of doses taken) and 'timing compliance' (p=0.028) (percentage of doses taken within 3 hours of the prescribed dosing intervals) at both weeks 12 and 24.

One RCT, **Rudd (2004)** [175], from the Cochrane updated review that was included in the evidence review on the effects of self-monitoring on adherence reported some results in regard to once-daily regimens compared to twice-daily regimens. This RCT assessed a system for patients to monitor their own blood pressure. Seventy-six patients received routine care while the intervention group (n=74) received an automated blood pressure device for use at home with management by a nurse care manager. The patients recorded their own blood pressure then the device printed these which were mailed to the nurse care manager in order to guide medicines. The adherence measures by a medicine event monitor were found to be statistically significant (80% for the intervention group and 69% for the control group, p=0.03). One of the outcomes found that once-daily regimens had higher

adherence 82% (s.d=28%) than twice-daily 69% (s.d=34%) or more frequently 49% (s.d=41%). None of these differences were statistically significant.

Update searches

From the conducted update searches, we retrieved two RCTs that were considered important as they would contribute to modifying the recommendations drafted for the topic of the impact of changes of dosing regimes on adherence to prescribed medicine. These were Molina (2007) and Parienti (2007).

The safety, efficacy and adherence to lopinavir/ritonavir (LPV/r) dosed OD or BID in antiretroviral-naive, HIV-1-infected subjects was evaluated in an RCT **Molina (2007)** [173]. A randomised, open-label, multicenter comparative study was conducted through 96 weeks of treatment. A total of 190 antiretroviral-naive subjects with plasma HIV-1 RNA above 1000 copies/ml and any CD4(+) T cell count were enrolled. Subjects were randomised (3:2) to LPV/r 800/200 mg OD (n=115) or 400/100 mg BID (n=75). Subjects received TDF 300 mg and FTC 200 mg OD. Adherence to LPV/r through 96 weeks was measured using MEMS((R)) monitors. Median baseline VL and CD4(+) T cell count were 4.8 log(10) copies/ml and 216 cells/mm(3), respectively. Prior to week 96, 37% (OD) and 39% (BID) of subjects discontinued, primarily due either to adverse events (17% OD, 9% BID) or to loss to follow-up or nonadherence (12% OD, 17% BID). The proportion of subjects with VL <50 copies/ml (57% OD, 53% BID; p=0.582 (ITT NC = F)), change in CD4 count (244 cells/mm(3) OD, 264 cells/mm(3) BID; p = 0.513), and evolution of resistance did not differ between groups through 96 weeks. Diarrhoea (17% OD, 5% BID, p=0.014) was the most common moderate or severe, study medicine-related adverse event. Adherence to LPV/r was higher for the OD group than the BID group and declined over time in both groups.

Parienti (2007) [176] aimed to determine the effect of once-daily dosing on adherence to nevirapine. This RCT was comprised of three-phase (3-month observational, 4-month randomised, 5-month interventional) open-label, clinical trial at four French academic medical centres during 2005-2006

among 62 chronically HIV-1- infected subjects with long-lasting viral suppression under a twice-a-day nevirapine-based antiretroviral combination. Participants were randomly assigned to switch to nevirapine 400 mg once-daily (n = 31) or continue nevirapine 200 mg twice-a-day (n = 31). After the randomised phase, participants had an opportunity to choose their antiretroviral dosage.

Fifty-two patients qualified for electronic data analysis. During the randomised phase, the mean adherence rate was not statistically significantly superior by 0.5% in once-daily versus twice-a-day dosing (p=0.68), adjusting for previous twice-a-day adherence rate (p<0.0001). Once-daily group increased days without dose (odds ratio (OR) 1.7; 95% CI 1.0, 2.8; p=0.04), adjusting for previous medicine interruptions (p<0.0001). In the longitudinal analysis, once-daily dosing was statistically significantly associated with at least two consecutive days without dose (OR 4.4; 95% CI 1.9, 10.3; p<0.001). The authors concluded that changing from twice to once-daily nevirapine did not improve adherence.

8.6 Effect of prescription charges on adherence to prescribed medicine

Related references	Evidence statements (summary of evidence)
Hirth (2008) [177]; Atella (2005) [178]	Some UK patients may have difficulty affording medicines. The most common strategies for patients with problems affording medicines is to delay the dispensing of medicines, to not visit the GP and to lower the dose below that prescribed to extend the duration of the prescription.

8.6.1 Evidence to recommendations

For general discussion of limitations of evidence see section 8.3

The GDG considered cost an important issue to address. The majority of patients do receive prescriptions free on the NHS but a substantial minority do not.

Most of the evidence for cost as a barrier to adherence comes from the US and these are not relevant to NHS settings. Only a few studies have been conducted in the UK. These indicate that for some patients costs are a concern. Cost concerns may also indicate doubts by the patient about the value of the prescription.

When cost is a concern for patients a variety of options are available each of which have advantages and disadvantages.

The GDG noted that there are a number of schemes in existence which aim to provide free or reduced cost of prescriptions e.g. prescription pre-payment certificates and exemption certificates.

Prescription length may be increased giving the patient longer prescription for the same cost but this may reduce the opportunity for review. Quite short dispensing time frames may be important for example when patients are suicidal or need careful monitoring of medicine and its effects. Instalment dispensing is possible for certain medicine items but in general it seems unreasonable to ask a patient to pay for each dispensing point. However the GDG was also mindful of the fact, that it might also be unreasonable for the pharmacist to make serial dispensings for a single dispensing fee. Costs and value of prescriptions should be considered not just at the point of prescribing but at all stages of the process.

The GDG did not consider it appropriate to make a specific recommendation on how healthcare professionals should act when cost is a problem for the patient as the response is likely to be dependent on patient circumstance and condition.

8.6.2   Methods of the evidence review

This question was included because although the issue of setting a prescription charge is outside the scope of this guideline, cost may be an issue for individual patients and the prescriber may be able to intervene if costs influence adherence.

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies – no restrictions on study design. However, due to the nature of the question, the requirement was that the studies needed to be conducted in the UK.

Types of participants- people prescribed medicine for a medical condition.

Duration of studies - no time limit specified.

Types of interventions - any interventions intended to assess the correlation between prescription charges and the impact on adherence to prescribed medicine.

8.6.3 Evidence review

Types of outcome measures – adherence to prescribed medicine, cost reducing strategies.

We retrieved one observational study **(Hirth 2008)** [177] that examined out of pocket medicine spending and cost-related medicine nonadherence among dialysis patients in twelve countries including the UK.

Data were gathered from 2002 to 2004 as part of the dialysis outcomes and practice patterns study (DOPPS), an observational study of haemodialysis practices and outcomes in twelve countries- Australia, New Zealand, Belgium, Canada, France, Germany, Italy, Spain, Sweden, United Kingdom, Japan, and the United States. A random sample of patients were selected, totalling n=7766. Of the selected 83 per cent who agreed to enrol and have their medical records abstracted, 85 per cent of these enrolled patients also completed the patient questionnaire. A total of 70 per cent of patients provided both medical and questionnaire data. Local currencies were converted to US Dollars.

Questionnaires and medical record abstraction techniques were standardised across countries and languages. Patient questionnaires were administered soon after recruitment. They were asked about the total out-of-pocket spending for prescription and over the counter (OTC) medicines in the previous month. They were also asked "Do you sometimes decide not to purchase medicines because of cost?" and to report their out-of-pocket spending for haemodialysis treatments.

Whilst the United States reported 86 per cent of out-of-pocket spending for medicines, only patients in Australia/New Zealand, Belgium, and Sweden

were statistically significantly more likely to face out-of-pocket spending, while those in France, Japan, Spain and the UK were statistically significantly less likely to do so.

Mean monthly spending for prescription and OTC medicines ranged from $8 in the UK to $114 to the United States. Among patients with medicine spending, only 10 per cent faced monthly costs greater than $30 in the United Kingdom, whereas 10 per cent incurred costs greater than $310 in the United States.

Observed cost-related nonadherence, indicated by the proportion of patients who reported that they sometimes did not purchase medicines because of cost, was statistically significantly less than expected in France, Japan, Spain, Sweden and the UK.

Nonadherence was associated with the percentage of patients reporting any out-of-pocket spending and the average out-of-pocket cost. Although the US had high out-of-pocket spending burdens, their nonadherence was still clearly higher than would be expected on the basis of the percentage facing any costs or the mean cost burden. On the other hand, Sweden and Belgium had lower levels of nonadherence than would be expected given either measure of out-of-pocket spending burden. The lowest nonadherence rates existing in France, Japan, Spain and the UK were correlated with low out-of-pocket spending.

Atella 2005 [178] aimed to explore how and to what extent costs incurred by patients influence their decision-making behaviour in accessing medicines, both in the UK and in Italy.

Based on findings from focus groups, a questionnaire was designed to assess medicine cost issues. As such, several hypotheses were tested regarding patients' decision-making behaviour and how it was influenced by health and socio-demographic status and the novel concept of a self-rated affordability measure. Patients were eligible if they had either dyspepsia or mild hypertension. They were sampled as successive patients who visited 51

physicians in Italy and 21 community pharmacists in the UK. Samples were drawn from the areas of Manchester and Rome. Of the 550 dyspepsia and 600 hypertension questionnaires distributed, 122 and 153 were returned- a response rate of 22.2% and 25.5%, respectively. In the UK, 296 dyspepsia and 277 hypertension questionnaires were distributed, targeting dyspepsia patients who bought OTC medicines, and dyspepsia and hypertension patients who had to pay prescription charges; 110 dyspepsia and 134 hypertension questionnaires were returned, giving a response rates of 37.5% and 48.4%. In both countries the majority of the respondents were not exempt.

The self-rated affordability measure showed that 70.3 per cent of the UK sample and 66.5 percent of the Italian sample had to think about the cost of medicines at least sometimes. Also, 24.3 per cent and 16.3 per cent, respectively said they always have to think about how much money they have available to spend when they obtain medicines. According to the results, the patient initiated strategy most commonly used by UK respondents with affordability problems is (1) to delay the dispensing of medicines until they get paid, (2) not visiting the GP to avoid incurring the cost of prescribed medicine and (3) reducing the dose below that prescribed to extend the course of medicine.

Affordability issues were also strong when examining the use of self-medicine strategies. The UK respondents were particularly cost conscious when considering the price of an OTC product before buying it, or they would ask for something cheaper if they could not afford a particular OTC product.

The authors point out that affordability seemed to play a more important role in the UK sample than in the Italian, however they do point out that Italian patients with dyspepsia were sampled only through GPs and may be those more severely affected and/or less likely to be disposed towards self medicine. Also, OTC products are much more expensive in relation to the prescription charge that they are in the UK where the prescription charge is high.

8.7   Does medicine packaging affect adherence?

Related references	Evidence statements (summary of evidence)
Medicine packaging	
Orton (2005) [179]	One systematic review found that unit-dose packaged medicines (blister packs and polythene bags with separate pockets compared to envelopes or bottles), as part of multi-component interventions showed higher adherence. However these results were drawn from trials with methodological limitations, one RCT with possible confounding and 3 quasi-RCT studies.
Schneider (2008) [180]	One RCT found that the use of blister packaging (Pill Calendar), for one medicine (lisinopril), compared to medicine in a bottle statistically significantly increased adherence.
Becker (1986) [181]	One RCT where all medicines were prepared together in a blister package, compared to receiving medicine in separate vials for each medicine, showed a statistically non-significant improvement in adherence to prescribed medicine.
Lee (2006) [182];	One RCT showed that blister packaging of multiple medicines as part of a multi-component intervention given to an elderly population (≥65 years) statistically significantly increased adherence to prescribed medicine.

8.7.1 Evidence to recommendations

For general discussion of limitations of evidence see section 8.3. The GDG considered the evidence review did not provide convincing evidence that medicine packaging per se increases adherence. The GDG recognised that individual patients may have practical difficulties in using medicines depending on packaging and considered that health care professionals should explore with patients whether the way in which a medicine is packaged causes difficulty and respond to individual problems.

8.7.2 Methods of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies - We initially included only randomised controlled trials (RCTs) of interventions to increase adherence. The excluded studies list from the Cochrane review was cross-referenced as we included studies with less than 80% follow-up of participants. After the GDG voiced concerns over the possibility of missing out important studies by only having included a small amount of studies, the search was redone to pick up any systematic review published after the Cochrane review search cut-off.

Types of participants - people prescribed medicine for a medical condition.

Duration of studies - six months follow up from the time of patient entry for long-term regimens for the RCTs. No time limit specified for short-term conditions.

Types of interventions - any interventions intended to change adherence to prescribed medicine. As the Cochrane review is presented by condition, we have used the evidence extracted in that review and reconfigured it by intervention.

Types of outcome measures - inclusion criteria (as defined in the Cochrane review) were expanded by including studies that used adherence as the only

outcome variable as opposed to adherence and treatment outcome variables. The excluded studies list of the Cochrane review was cross-referenced to ensure that no potentially relevant study was missed out.

8.7.3 Evidence review

8.7.3.1 Effect of medicine packaging on adherence

Medicine packaging

In this evidence review the GDG were wishing to find out whether the packaging that medicine came in would affect adherence. The only relevant systematic review that we found was a Cochrane review by Orton (2005). It looked at blister packs and sectioned polythene bags for the medicine. Other RCTs that we looked at included blister packs that had multiple medicines in a blister pack that were produced specifically for the patient. It should be noted that these technologies are not available in the UK at present and the evidence did not address the question the GDG were most interested in.

Blister packaging is where the medicines are sealed in a blister pack, which often has a calendar of days of the week or month. One blister can hold either one single medicine or can be a combination of several medicines.

Systematic Reviews

One Cochrane review **Orton (2005)** [179] that aimed to assess the effects of unit-dose packaged treatment and treatment adherence in people with uncomplicated malaria was retrieved. Any type of programme that included unit-dose packaging of antimalarial medicines packed in units of a single dose was incorporated in the review. Treatment adherence was a secondary outcome, however all four included studies measured it.

Interventions and control arm groups had to received the same antimalarial medicine and any other intervention. The interventions that were assessed in this systematic review ranged from labelled and boxed blister packs of chloroquine and primaquine tablets and capsules, simple labelled and

sectioned polythene bags of chloroquine tablets, tablets or capsules in paper envelopes or loose and chloroquine syrup in bottles.

Three quasi RCTs and one cluster RCT met the inclusion criteria, and overall trials were of poor methodological quality.

A meta-analysis of two trials (with 596 participants) showed that participant reported treatment adherence was higher with blister-packed tablets compared with tablets in paper envelopes (RR 1.18, 1.12 to 1.25). Two trials using tablets in sectioned polythene bags as the intervention also reported an increase in participant reported treatment adherence: in one study (cluster RCT) it was compared with the tablets in paper envelopes whilst the other trial compared it with syrup in bottles (RR 2.15, 1.76 to 2.61; 299 participants).

It appears that unit-dose packaging medicines (in combination with prescriber training and patient information) was associated with higher participant reported treatment adherence, however this conclusion is drawn from trials with methodological limitations.

Heneghan (2006) [183] conducted a systematic review of reminder packaging which included blister packaging. This review is already included in the 'multi-compartment medicine systems' key clinical question and only one blister package RCT with adherence data was included in the Heneghan review, therefore we have not included Heneghan in the packaging question. The blister pack RCT (with adherence outcomes) from Heneghan (2006) has been included for this question (see Becker, 1986).

Randomised Controlled Trials

Becker (1986) [181] from the Cochrane review delivered an intervention whereby patients aged 20 to 80 years were assigned to the experimental group received all their medicines in the special packaging format (all pills taken together were packaged in a single plastic blister sealed with a foil backing on which was printed the day of the week and the time of day at which each medicine was to be taken). One hundred and eighty patients were

included in the study. Patients in the control group received all of their antihypertensive medicines in the conventional pill vials (separate vials for each pill that were labelled with the medicine name, the dosage, the medicine instructions, and the physician's name). All medicines for both groups were provided free of charge to ensure that all patients would receive their medicines. This study was conducted in the USA. No statistically significant effects on adherence were reported.

Schneider (2008) [180] conducted a randomised controlled trial to assess the impact of one medicine packaging type on adherence and treatment outcomes of older patients. The study was conducted at 3 sites in Tucson and Columbus in the USA. 85 participants aged 65 years or older, prescribed lisinopril (antihypertensive medicine) were randomised to receive daily-dose blister packaged medicine (pill calendar) as the intervention compared to traditional bottles of loose tablets as the control group. Patients returned for refills every 28 days during a 12 month period where the pharmacist would record the time between prescription refills for the medicine and any study-related problems. At 6 and 12 months after enrolling the patients visited the physician to find out blood pressure management; the occurrence of morbidity in the past 6 months e.g. angina, myocardial infarction and stroke; and any medical services they had required in the past 6 months e.g. hospitalisations or emergency department visits. Medical charts were reviewed by two pharmacists to gather this information. The percentage of times prescriptions were refilled on time (within 5 days before or after due date) were statistically significantly higher 80.4% (s.d=21.2) for the intervention group than the control group, 66.1% (s.d=28), p=0.012. The medicine possession rate (the sum of the day's supply for all prescriptions received during the study divided by the number of days between the first and last prescription dispensed) was also statistically significantly higher for the intervention group, 0.93 (s.d=11.4) and 0.87 (s.d=14.2) for the control group, p=0.039. No differences were found between the groups for systolic blood pressure and diastolic blood pressure measures.

Lee (2006) [182] compared a comprehensive pharmacy care program which was delivered to one group for 3-8 months and a second group for 3-14 months in 200 patients aged 65 years or over, taking four or more chronic medicines daily with positive results. The first group returned to usual care after 8 months. The care program consisted of 3 elements, including individualised education on medicines; medicines dispensed using an adherence aid (blister packs) and regular follow-up with clinical pharmacists every 2 months. This study was conducted in the USA.

Mean baseline adherence overall was 61.2% (s.d=13.5%) with an overall level of adherence of 96.9% at 8 months of intervention. At 14 months, medicine adherence was 95.5% (s.d=7.7%) in the continued intervention group and 69.1% (s.d=16.4%) in the control group (p<0.001). Proportions of people who had at least 80% adherence rates were 97.4% in the intervention group and 21.7% in the control group (p<0.001).

8.8 Does the use of multi-compartment medicine systems increase adherence to prescribed medicine?

Related references	Evidence statements (summary of evidence)
Heneghan (2006) [183]	A high quality systematic review suggests that some types of multi-compartment medicine systems may improve adherence to prescribed medicine. It should be noted that only four RCTs were multi-compartment compliance aids which reported adherence data. These RCTs were classed as having a high risk of bias. Some of these RCTs were part of a multi-component intervention.
Henry (1999) [184]	One RCT showed that a multi-compartment medicine system as part of multi-component intervention showed no statistically significant effects on adherence.
Peterson (1984) [185]	One RCT showed that that a multi-compartment medicine system as part of a multi-component intervention showed statistically significant effects on adherence to medicine.

8.8.1 Evidence to recommendations

For general discussion of limitations of evidence see section 8.3.

Despite the frequent use of multi-compartment devices that are refilled regularly by pharmacists and individuals, there was little evidence on their use. For patients who have practical problems in managing complex regimes or who may be forgetful these devices may have a value. The GDG considered that many individuals develop their own strategies and that the

evidence on these devices was not strong enough to make recommendations for widespread use.

8.8.2   Methods of the evidence review

This review was originally titled 'does the use of dosette boxes increase adherence to prescribed medicine'. Dosette box is an example of a device which holds a patient's medicine and is labelled with periods of time. Although the term is derived from a particular brand of device it is widely used in routine clinical practice. The evidence search using a variety of terms returned no studies. After consultation it was brought to our attention that devices like dosette boxes may be classified under different headings and that some researchers label them as 'reminders' or as 'packaging'. We therefore re-examined the papers included in the packaging review and reminder reviews and extracted those relevant to dosette-type devices. The review by Heneghan (2006) and some RCTs/systematic reviews which had been incorrectly placed with the packaging and reminder questions are now relocated to the question. These we have termed multi-compartment medicine systems although there is no agreed term in the published literature. The term 'dosette' is no longer used in the final recommendations. The original search terms matched the terms needed for this restructured multi-compartment medicine system question. For example the search terminology included 'dosette', 'nomad' or 'manrax' 'monitored dosage system' and 'compliance aid'.

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies – no restrictions on study design.

Types of participants- people prescribed medicine for a medical condition.

Duration of studies - no time limit specified.

Types of interventions - any interventions intended to assess the correlation between the use of multi-compartment medicine systems and the impact on adherence to prescribed medicine.

8.8.3   Evidence review

Multi-compartment medicine systems

Reviews differed in the terminology of these systems and also grouped multi-compartment medicine systems together with packaging methods such as blister packaging.

Multi-compartment medicine systems are devices which hold a patients' medicine (single and multiple medicines) and are labelled with periods of time (day/days of the week/month). They can be re-used and can be filled by the pharmacist or by the patient themselves. This differs from the evidence review of blister packaging as this is a device rather than a type of packaging. Some studies included in the reviews considered the use of non-reusable blister or compartment packaging which was done by individual pharmacists for individual patients.

Systematic Reviews

One high quality systematic review by **Heneghan (2006)** [183] aimed to determine the effects of 'reminder packaging' to increase patient adherence with self-administered long-term medicines.

The systematic review included eight studies containing 1137 participants. All types of setting were included and no age limits were set. Studies where direct observation of therapy occurred through a health professional were excluded. Interventions that were included required a medicine system for the day of the week or the time that the medicine was to be taken, and it had to form part of the packaging.

The primary outcome of importance was adherence to medicine which was measured by pill counts and/or self-reporting. Three of the RCTs included in the review did not have any adherence data, these were Simmons (2000),

Binstock (1988) and Winland-Brown (2000). Simmons (2000) was the only RCT from Heneghan to meet all the quality criteria and to be judged as having a low risk of bias.

The authors refer to the findings under the term 'reminder packaging'. Therefore we have split this into two categories of packaging – blister packs and multi-compartment medicine systems. Blister packaging is discussed in the section on packaging.

Heneghan (2006) conducted a combined analysis of the studies of pill count (the 6 interventions using multi-compartment medicine systems, within 4 RCTs) and found that there was a statistically significant increase in the percentage of pills taken within the groups that had 'reminder packaging', Weighted mean difference 11% (95% CI 6% to 17%, p<0.0001). Heneghan (2006) concluded that 'reminder packaging' (multi-compartment medicine systems and blister packaging) is a simple method for improving adherence but can be problematic and have errors. They state that, while awaiting further trials, there is justification for use of these systems with patients where need is identified.

Randomised controlled trials from the Heneghan (2006) study

Azrin (1998) conducted a RCT with 39 participants who had mental illness, with a mean age of 38.5 years in Florida, USA. One group received a pamphlet of information on types of medicine, their action, efficacy, potency and side effects. Another group received a 'guidelines to taking medicines' pamphlet. All participants received a pill box with 28 compartments (4 time periods/day). The guideline pamphlet covered the correct use of the pill box. There was a change in adherence to medicine (proportion of pills taken) from pill counts and self-reported measures.

Huang (2000) conducted a RCT of 184 participants (aged 20 to 80 years) who were to take vitamin pills for two months. The intervention group received medicines in bottles and a pill organiser with seven compartments (for each day of the week). The participants had to remove the pills from the bottles and

place them in the organiser. The control group received the pills in two bottles and did not receive an organiser.

Skaer (1993) NIDDM-a conducted a RCT of 258 non-insulin dependent diabetes mellitus (NIDDM) patients (aged <65 years) from South Carolina, USA receiving Medicaid benefits. The intervention group received standard pharmaceutical services and with every prescription refill request they were provided with a sequentially numbered 30-day supply inventory tray with easy access compartments. The control group received standard pharmaceutical care.

Skaer (1993) NIDDM-b conducted a RCT with 258 medicaid beneficiaries (aged <65 years) with NIDDM which had not been previously treated. The intervention group received pharmaceutical care, unit of use packaging and a medicine refill reminder 10 days before their refill date.The control group received the pharmaceutical care and mailed medicine refill reminders.

Skaer (1993)a conducted a RCT of 304 medicaid patients (aged <65 years) who had mild to moderate hypertension. The intervention group received pharmaceutical care and unit of use packaging (30-day supply inventory tray with easy access compartments). The control group received standard pharmaceutical care.

Skaer (1993)b conducted a RCT of 304 medicaid beneficiaries (aged <65 years) who had mild to moderate hypertension. The intervention group received standard pharmaceutical care, unit of use packaging and a mailed medicine refill reminder ten days before their refill date. The control group received standard pharmaceutical care and mailed medicine refill reminders.

It should be noted that the four Skaer studies represent only two randomised controlled trials.

Randomised Controlled Trials (not included in the systematic reviews)

Henry (1999) [184] from the Cochrane review delivered an intervention where verbal advice on medicine use and possible side-effects were employed along

with information sheets on the treatments and medicines with the dose-dispensing unit. The control group were given treatment only, along with verbal advice and information sheets. A total of 119 patients were included. Mean age of patients was 58 years for the control group and 57 for the intervention group. Compliance in intervention group patients was also encouraged by a phone call 2 days after the start of therapy. This study was conducted In Australia. No statistically significant effects on adherence were reported.

In **Peterson's (1984)** [185] (from the Cochrane review) RCT, the intervention group received several adherence-improving strategies: patients were counselled on the goals of anticonvulsant therapy and the importance of good adherence in achieving these goals; a schedule of medicine-taking was devised that corresponded with the patient's everyday habits; patients were given a copy of an educational leaflet; each patient was provided with a 'dosette' medicine container and counselled on its utility; patients were instructed to use a medicine/seizure diary; and patients were reminded by mail of upcoming appointments and of missed prescription refills. The control group received none of these interventions. Patient compliance improved statistically significantly with the intervention group patients. At follow-up the proportion of compliant patients in each group differed statistically significantly (according to their prescription refill frequencies), 88% of the intervention group and 50% of the control group were considered compliant (chi-square=8.79, df=1, p<0.01). Fifty three adults and teenagers were enrolled in the study, and the median age was 35 years for the control group and 28 years for the intervention group. The study was conducted in Australia.

8.9 Does medicine formulation affect adherence?

Related references	Evidence statements (summary of evidence)
Bangalore (2007) [186]	One highly biased systematic review suggests that fixed dose combination compared to free medicine component regimen may increase adherence to prescribed medicine.
Brown 1997 [170]	One RCT showed that controlled release medicine along with simplified dosing compared to regular medicine may increase adherence to prescribed medicine.

8.9.1 Evidence to recommendations

For general discussion of limitations of evidence see section 8.3

The GDG considered the evidence review did not provide convincing evidence that changes to medicine formulation will improve adherence. Changes to medicine formulation should be considered with changes to dosing as a response to individual patient problems only.

8.9.2 Methods of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies - We initially included only randomised controlled trials (RCTs) of interventions to increase adherence. The excluded studies list from the Cochrane review was cross-referenced as we included studies with less than 80% follow-up of participants. After the GDG voiced concerns over the possibility of missing out important studies by only having included a small

amount of studies, the search was redone to pick up any systematic review published after the Cochrane review search cut-off.

Types of participants - people prescribed medicine for a medical condition.

Duration of studies - six months follow up from the time of patient entry for long-term regimens for the RCTs. No time limit specified for short-term conditions.

Types of interventions - any interventions intended to change adherence to prescribed medicine. As the Cochrane review is presented by condition, we have used the evidence extracted in that review and reconfigured it by intervention.

Types of outcome measures - inclusion criterion (as defined in the Cochrane review) was expanded by including studies that used adherence as the only outcome variable as opposed to adherence and treatment outcome variables. The excluded studies list from the Cochrane review was cross-referenced to ensure that no potentially relevant study was missed out.

8.9.3 Evidence review

8.9.3.1 Does medicine formulation affect adherence?

Systematic Reviews

The possibility of bias was assessed to be high in a systematic review by **Bangalore (2007)** [186] which included RCTs and retrospective reviews of data bases. Nine studies were combined in a meta-analysis which included three RCTs and four retrospective data bases of pharmacy claims. There was marked heterogeneity in the compliance measures among the studies evaluated and the patient group had different conditions which were being treated. In the meta-analysis a total of 11,925 patients on fixed dose combination were compared against 8317 patients on free medicine component regimen. Fixed dose combination resulted in a 26% decrease in the risk of non-compliance compared with free medicine component regimen (pooled RR 0.74 (CI 0.69-0.80; $p < 0.0001$). There was no evidence of

heterogeneity in this analysis (p=0.07). A subgroup analysis of the four studies on hypertension showed that fixed dose combination (pooled RR 0.76 CI 0.71-0.81; p<0.0001) decreased the risk of medicine non-compliance by 24% compared with free medicine combination regimens. Due to methodological concerns about the conduct of the meta-analysis, the results of this study should be viewed with caution.

Randomized Controlled Trials

Brown (1997) [170] from the Cochrane review looked at the effect of different formulations as they compared regular niacin versus polygel controlled release niacin. All patients received lovastatin 20mg, colestipol 10g, and niacin 500mg for 12 months, with dosage adjustment to target cholesterol of 150 to 175mg/dl, and to minimize side effects. Twenty-nine male participants were enrolled aged ≤65 years At 12 months, patients were randomly assigned to 1) continue with regular niacin at a dose identical to that established during the 12 month dose-finding period, or 2) change to polygel controlled-release niacin at that daily dosage, but given twice rather than 4 times/day. At 20 months, groups 1) and 2) were reversed (crossover). This study was conducted in the USA. Adherence was statistically significantly greater for the controlled-release preparation.

8.10 Do reminders (and what types of reminders, text messaging etc) increase adherence to prescribed medicine?

Related references	Evidence statements (summary of evidence)
Stewart (2005) [187]; Urien (2004) [188]; Piette (2000) [189]	Three RCTs show that a reminder given via a telephone call in a multi-component intervention can increase adherence to prescribed medicine.
Beaucage (2006) [190]	One RCT showed no statistically significant results on the effect of a reminder given via a telephone call in a multi-component intervention in increasing adherence to prescribed medicine
Hamet (2003)[191]; Peterson (1984) [185]	There is conflicting evidence on the effect of reminders via mail in a multi-component intervention in increasing adherence to prescribed medicine.
Vrijens (2006) [192]; Mannheimer (2006) [193]; Sackett (1975) [194]	There is conflicting evidence on the effect of electronic reminders in a multi-component intervention in increasing adherence to prescribed medicine.
Guthrie (2001) [195]	One RCT showed that using a combination of postal and telephone reminders in a multi-component intervention showed no effect on adherence to prescribed medicine.

8.10.1 Evidence to recommendations

For general discussion of limitations of evidence see section 8.3

The type of reminders varied – telephone, mail, electronic or a combination of telephone and mail. The benefit of any type of reminder was not clear from the available evidence. The GDG did not consider the evidence sufficient to make any recommendations about reminders.

8.10.2 Methods of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies - randomied controlled trials (RCTs) of interventions to increase adherence. The excluded studies list from the Cochrane review was checked as we have included those studies with less than 80% follow-up of participants.

Types of participants - people prescribed medicine for a medical condition.

Duration of studies - six months follow up from the time of patient entry for long-term regimens. No time limit specified for short-term conditions.

Types of interventions - any interventions intended to change adherence to prescribed medicine. As the Cochrane review is presented by condition, we have used the evidence extracted in that review and reconfigured it by intervention.

Types of outcome measures - inclusion criterion (as defined in the Cochrane review) was expanded by including studies that used adherence as the only outcome variable as opposed to adherence and treatment outcome variables. The excluded studies list of the Cochrane review was cross-referenced to ensure that no potentially relevant study was missed out.

8.10.3 Evidence review

8.10.3.1 Telephone reminders

Stewart (2005) [187] compared four once-monthly educational sessions, the prescription of a home-based walking program and once-monthly phone calls

with four once-monthly educational sessions, the prescription of a home-based walking program without once-monthly phone calls in patients attending a hypertension clinic with positive results at week 24 but not 36. Sample size was comprised 83 participants. During the phone calls patients (or a family member) were asked about the exercise program and reminded about diet and medicine. In total 5 (pairs) of telephone calls (to patient and family member) were made once monthly over 24 weeks by a physiotherapist. This study was conducted in South Africa.

At week 24 statistically significantly more patients in the group receiving telephone calls (65%) were taking their medicines as prescribed compared to the group not receiving telephone calls (44.7%, p=0.05), however, there was no difference between the groups at week 36 (82.4% vs 86.7%) [187].

Urien (2004) [188] compared a telephone-delivered intervention plus educational advice with educational advice alone in patients receiving antibiotic treatment. The sample was comprised of 128 participants aged ≥18 years. The telephone call was undertaken on the 4th day after the start of treatment, when the first box of antibiotics should have been finished. The patient was advised to continue the treatment according to the dosage and number of days that had been prescribed. The patient was also reminded that although he or she may feel better or even cured, the treatment was to be continued for 10 days. This study was conducted in Spain.

Adherence was statistically significantly higher in the intervention group (78.3%) than in the control group (54.1%) (p=0.005) [188].

Beaucage (2006) [190] compared a pharmacist telephone intervention with usual care in patients on antibiotic treatment with negative results. A telephone call was made to patients in the intervention group by a pharmacist 3 days into treatment. The pharmacist asked about the patient's general condition, on the presence of adverse effects and the participants understanding of dosing. The pharmacist emphasised the importance of adherence and offered motivation to the patient. The patients were offered an opportunity to ask questions and were given the pharmacist's contact details

in case they wanted to make contacted their pharmacist at a later time. This study was conducted in Canada.

Mean adherence to treatment was 94% (s.d=9%) and 94% (s.d=12%) in the intervention and control groups respectively (p=0.803). The proportion of patients with less than 80% adherence was similar in the two groups (Intervention group: 8%, control group: 9%).

Piette (2000) [189] compared a telephone intervention with usual care in patients with diabetes (n=280) with positive results. Patients were excluded if they were above 75 years of age. The intervention consisted of, "…a series of automated telephone assessments designed to identify patients with health and self-care problems (TeleminderModel IV automated telephone messaging computer). Calls were made on a bi-weekly basis, up to 6 attempted calls, and involved a 5 to 8-minute assessment. During each assessment, patients used the touch-tone keypad to report information about self-monitored blood glucose readings, self-care, perceived glycaemic control, and symptoms of poor glycaemic control, foot problems, chest pain, and breathing problems, with automated prompts for out-of-range errors. The automated telephone calls were also used to deliver, at the patient's option, 1 of 30 targeted and tailored self-care education messages at the end of each telephone session. Patients only received a 1-page instruction sheet on the use of the phone. Each week, the automated assessment system generated reports organised according to the urgency of the reported problems, and a diabetes nurse educator used these reports to prioritise contacts for a telephone follow-up. During follow-up calls, the nurse addressed problems reported during the assessments and provided more general self-care information. After several months, intervention group patients were offered additional automated self-care calls that focused on glucose self-monitoring, foot care and medicine adherence. In the medicine adherence part of these sessions, patients were asked about their adherence to insulin, oral hypoglycaemic medicines, antihypertensive medicines, and antilipidemic medicines. For each type of medicine, patients without adherence problems received positive feedback and reinforcement. Patients reporting less than optimal adherence were asked

about specific barriers and were given advice from the nurse about overcoming each barrier. The nurse was located outside the clinic and had no access to medical records other than the baseline information collected at enrolment and her own notes. She did not have any face-to-face contact with patients. The nurse addressed problems raised by patients in the automated calls and also gave general self-care education. The nurse also checked on patients who rarely responded to automated calls. A small number of patients initiated calls to the nurse by a toll free number. She referred these to the primary care physician as appropriate [196]. This study was conducted in the United States.

Compared with usual care, patients in the intervention group reported fewer problems with medicine adherence ($p< 0.003$).

8.10.3.2 Mail reminders

Hamet (2003) [191] compared the Avapromise intervention (designed to modify behaviour by medicine adherence through reinforcement and lifestyle modification) with usual care in patients with high blood pressure. This was a study that comprised a total of 4864 participants. The ages of participants ranged from 16 to 89 years. The intervention was made up of two elements that were delivered together. The first element attempted to reinforce medicine behaviours by using medicine reminder letters, blood pressure diaries and telephone nurse counselling sessions. The second element addressed lifestyle management through educational brochures. Patients assigned to the intervention group were mailed the material at one, two, three, four, six and 12 months. This study was conducted in Canada.

A total of 25.4% (95% CI 23.7 to 27.2) of patients discontinued their treatment from the intervention group and 25.5% (95% CI 23.8 to 27.3) from the control group ($p=0.94$). There was no statistically significant difference in the duration of Irbesartan compliance between the treatment groups [191].

In **Peterson's (1984)** [185] (from the Cochrane review) RCT, the intervention group received several adherence-improving strategies: patients were

counselled on the goals of anticonvulsant therapy and the importance of good adherence in achieving these goals; a schedule of medicine-taking was devised that corresponded with the patient's everyday habits; patients were given a copy of an educational leaflet; each patient was provided with a 'dosette' medicine container and counselled on its utility; patients were instructed to use a medicine/seizure diary; and patients were reminded by mail of upcoming appointments and of missed prescription refills. The control group received none of these interventions. Patient compliance improved statistically significantly with the intervention group patients. At follow-up the proportion of compliant patients in each group differed statistically significantly (according to their prescription refill frequencies), 88% of the intervention group and 50% of the control group were considered compliant (chi-square=8.79, df=1, p<0.01). Fifty three adults and teenagers were enrolled in the study, and the median age was 35 years for the control group and 28 years for the intervention group. The study was conducted in Australia.

8.10.3.3   Mail and telephone reminders

Guthrie (2001) [195] delivered an intervention involving postal and telephone reminders regarding coronary risk reduction and medicine compliance, which were sent during the first 2 months of pravastatin treatment, or usual care. This was a large study that comprised a total of 13,100 participants. Mean age was 58.0 years. Both groups received reminder postcards at 4 and 5 months, in addition to counselling by physicians about coronary risk reduction. At study discontinuation, patients completed and mailed (to the program-coordinating centre) questionnaires concerning compliance with care, as well as self-reported adoption of other lifestyle modifications. This study was conducted in the USA. Neither early reminders nor baseline patient characteristics were statistically significantly associated with reported pravastatin compliance rates.

8.10.3.4   Electronic reminders

Vrijens (2006) [192] compared a supportive intervention program with usual care in patients who had been taking atorvastatin with positive results. Four

hundred and twenty nine participants aged >18 years entered the study. As part of the supportive intervention program participants were supplied with a 'beep-card' that reminded the patient of the dosing time, and also gave educational reminders. The supportive intervention program also provided patients with a medicine review by the patients' pharmacist of their electronically compiled dosing history (through MEMs). At each follow-up visit the pharmacist delivered an educational message, updated the patients' compliance passport and analysed with the patient their electronically compiled dosing history over the previous month/3 months (depending on the gap between follow-up appointments). Baseline adherence was statistically significantly higher in the intervention group compared to the control group (96.43% vs. 94.33%, p=0.003). At 12 months, the intervention group had an increased adherence of 6.5% compared to the control group (95.89% vs. 89.37%, p<0.001). The analyses were stratified by baseline compliance and language region. Over time, the difference between groups increased, with approximately 17% difference in adherence between groups at 300 days. 13% (n=25) of the intervention group discontinued medicine before 300 days, compared to 25% (n=51) in the control group. Persistence was statistically significantly higher in the intervention group compared to the control group (87% vs. 74%, p=0.002). This remained statistically significant when adjusted for multiple baseline variables. This study was conducted in Belgium [192].

In a study conducted by **Sackett (1975)** [194] (from the Cochrane review), subjects in one of the interventions (augmented convenience) groups visited company physicians, rather than their family physicians, for hypertensive and follow-up care during paid working hours. Two hundred and thirty Canadian steelworkers were enrolled. The ages of the participants were not reported in the study. The second intervention, mastery learning, aimed to give the facts about hypertension, its effects upon target organs, health, and life expectancy, the benefits of antihypertensive therapy, the need for adherence with medicines and some simple reminders for taking pills (which was provided in a slide-tape format, and reinforced by a secondary-school graduate). No

statistically significant results were reported. This study was conducted in Canada.

Mannheimer (2006) [193] conducted a cluster randomised controlled trial (2x2 factorial design) to assess two interventions to increase adherence in 928 patients who were taking anti-retroviral therapy in the USA. One intervention is the Medicine Manager (MM) which involved a trained research staff member working with the participants individually to provide tailored adherence support according to a standardised protocol, identifying and addressing information, motivation and skills for antiretroviral adherence (using detailed questionnaires). The second intervention was the electronic medicine reminder system, a small portable alarm (ALR) which was programmed to flash and sound when antiretroviral doses were due. Participants were followed up with assessments at 1 and 4 months after randomisation and 4 months thereafter. The MM group had statistically significantly higher reporting of 100% adherence over time compared to non-MM interventions (OR=1.42, p<0.001). There were no statistically significant differences between the ALR group and the non-ALR groups for adherence.

8.10.3.5 *Type of reminders used not stated*

De Geest (2006) [197] compared a nurse-led intervention and usual care with usual care alone in patients who had undergone a kidney transplant with negative results. This was a small study that comprised a total of 18 participants aged > 18 years. The intervention group received one home visit and three telephone interviews, one at the end of the month for three consecutive months. During the home visit printouts were discussed with the patient for problem detection, and adherence goals were set. All patients received self-efficacy interventions. Nurses also implemented additional educational, behavioural (e.g. the use of reminders) and/or social support interventions if they felt this would help the patient. Telephone calls served to discuss adherence in the previous month, to check on health status, and discuss and change, if appropriate, adherence interventions. This study was conducted in Switzerland.

Adherence increased in both groups over the first 3 months (p=0.04). The overall difference between groups was statistically non-significant at 3 months (p=0.31) and at 9 months (p=0.58) with a gradual decline over the total 9 months to a level still higher than initial levels [197].

8.11 Is there any evidence on interventions that aim to minimize side-effects in order to increase adherence?

Related references	Evidence statements (summary of evidence)
Rickles (2005) [198]; Collier (2005) [199]; Kemp (1998) [200]	There is conflicting evidence with regard to whether discussing side effects, as part of a multi component intervention, increases adherence.
Rathbun (2005) [201]; Chaplin (1998) [202]; Canto De Cetina (2001) [203]; Tuldra (2000) [204]; Peveler (1999) [205]	There is conflicting evidence with regard to whether educating patients about side effects, as part of a multi-component intervention, increases adherence.
Howland (1990) [206]	One RCT showed that informing patients about side effects did not have a statistically significant effect on adherence.
Vivian (2002) [207]; Finley (2003) [208]; Katon (2002) [209]	There is conflicting evidence with regards to whether giving an intervention deliverer (e.g. a pharmacist) the power to adjust a patient's medicine and/or dosage, as part of a multi component intervention, increases adherence.
Chisholm (2001) [210]; Adler (2004) [211]	There is conflicting evidence with regard to whether giving an intervention deliverer (e.g. a pharmacist) the power to make recommendations about the treatment to the patient's practitioner, as part of a multi component intervention, increases adherence.

8.11.1 Evidence to recommendations

For general discussion of limitations of evidence see section 8.3

Interventions relating to side effects primarily involve providing information for patients on side effects. No single way of providing information on side effects with a view to increase adherence to prescribed medicine can be recommended. This is mainly due to the evidence not assessing the impact of minimising side effects independently, thus not being able to ascertain their true effect.

The GDG considered that there are a number of ways to manage side effects to support patient adherence. These include adequately informing patients about side effects, exploring how a patient wants to manage side effects, reducing the dose of medicine and changing the medicine to an alternative.

8.11.2 Methods of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies - randomised controlled trials (RCTs) of interventions to increase adherence. The excluded studies list from the Cochrane review was checked as we have included those studies with less than 80% follow-up of participants.

Types of participants - people prescribed medicine for a medical condition.

Duration of studies - six months follow up from the time of patient entry for long-term regimens. No time limit specified for short-term conditions.

Types of interventions - any intervention intended to change adherence to prescribed medicine. As the Cochrane review is presented by condition, we have used the evidence extracted in that review and reconfigured it by intervention.

Types of outcome measures – inclusion criteria (as defined in the Cochrane review) were expanded by including studies that used adherence as the only outcome variable as opposed to adherence and treatment outcome variables. The excluded studies list of the Cochrane review was cross-referenced to ensure that no potentially relevant study was missed out.

8.11.3 Evidence review

Although a number of RCTs were found which addressed side effects, we did not find many where the interventions' sole purpose was to address side effects. Within the RCTs which did address side effects there was a lot of variability in how they did this and to what extent side effects were a focus of the intervention. What follows is a summary of the RCTs which addressed side effects with information on interventions limited to those parts of the study which addressed side effects. For further details please see evidence tables for the RCTs retrieved from update searches, or the Cochrane review.

8.11.3.1 Discussing side effects with patients

RCTs were excluded from this section if side effects were only discussed, and if no further details were given on how to educate the patients in managing their side-effects with a view to increase adherence. Other RCTs were excluded if addressing side effects was potentially part of a multi-component intervention but when the actual decision to address side effects was the choice of the intervention provider (therefore meaning it was impossible to tell how many patients in the intervention group had side effects addressed and how many did not have this issue addressed).

3 RCTs addressed side effects by clearly discussing them with patients. **Rickles (2005)** [198] had pharmacists address adverse events during telephone calls in 98 patients with a mean age of 38 years. The pharmacist could probe or explain issues not understood by the patient and make recommendations. The intervention had positive effects. The difference at six months in adherence with the rate of missed doses was statistically significantly lower in the intervention group (30.3%, s.d=36.4 vs. 48.6%, s.d=39.2, p=<0.05). This study was conducted in the USA. **Collier (2005)** [199] had nurses address

participants' medicine-related behaviour and barriers to adherence during telephone calls in 282 patients. Advice around side effects was offered. Over 24 months, rates of adherence were high in both groups (>72% reported at least 95% adherence). No difference was seen between groups (OR 0.86, 95% CI 0.57 to 1.29). This study appears to have been conducted in the USA. **Kemp (1998)** [200], an RCT from the Cochrane review, as part of "compliance therapy", had 2 sessions where intervention group participants focused on symptoms and the side effects. This study had 74 participants. The mean age in the intervention group was 34 years (s.d=10.6) and 37 years (s.d=11.9) in the control group. This study was conducted in the UK.

Patients receiving compliance therapy demonstrated higher adherence ratings (p < 0.001) than control group patients.

8.11.3.2 Educating patients and follow-up

5 RCTs addressed side effects through educating the patient about them and then following up on this education.

Rathbun (2005) [201] provided patients with a mean age of 38 years with education about adverse-event management strategies, among other things. A total of 43 patients were included in this study. Telephone follow-up was provided to identify early problems. At week 28, adherence rates were 74% (s.d=31%) in the intervention group and 51% (s.d=41%) in the control group (p=0.080, difference between groups 23%, 95% CI: 1% to 44%). Mean decline in adherence between weeks 4 and 28 were 12% (p=0.15) in the intervention group and 22% (p=0.002) in the control group. Patients in the intervention group were more likely to take their medicine at the prescribed dosing schedule: at 4 weeks, 69% in the intervention group vs 42% in the control group (p=0.025) and at 28 weeks, 53% in the intervention group vs 31% in the control group (p=0.046). No statistically significant difference was seen between the groups based on patient self-report (94% vs 89% intervention vs control, p=0.51). This study was conducted in the USA.

Chaplin (1998) [202], an RCT from the Cochrane review, had intervention group participants, "…participate in a discussion about the risks and benefits of neuroleptic medicines based on individual semi-structured educational sessions with reference to a standardised information sheet. The patients were asked whether they had heard of tardive dyskinesia. The common movements of TD were modelled and the patients were asked whether they thought they had the condition or had seen others with it. They were informed that they were receiving an antipsychotic medicine and were given information about extrapyramidal symptoms and TD, its risk factors, prevalence, treatment, potential irreversibility and the 1% risk of TD in non-antipsychotic-treated patients. They were told that gradual discontinuation of antipsychotic medicine was the best way to prevent the condition but if done abruptly carries a high risk of relapse and of precipitating TD. It was stated that the optimum maintenance treatment, taking into account its risks and benefits, was to use the lowest dose of antipsychotic medicine that would keep them well. Most importantly, they were asked not to make any changes to their treatment without discussion with their psychiatrist. Finally, they were given the opportunity to ask questions in an informal interactive session lasting 30 minutes, and were given an information sheet for reference" [196]. This study included 56 participants (age range not given) and was conducted in the UK. The intervention did not increase adherence relative to the control condition.

Canto De Cetina (2001) [203], an RCT from the Cochrane review, had women in their intervention group (counselling group) receive, "…a structured pre-treatment counselling with indications about the mode of action of DMPA, the common side effects of the medicine, including the possibility of irregular menstrual periods, heavy bleeding, spotting, and amenorrhea. To mentally prepare users for potential side effects, it was stressed that these side effects would be not detrimental to their health. These indications were repeated at each follow-up visit" [196]. This study included 350 participants. The mean age in the counselling group was 33.9 years with a 20-35 range and 34 years in the control group with also a 20-35 range. This study was conducted in

Mexico. There was a positive effect of the intervention in terms of cumulative termination rates.

Tuldra (2000) [204], an RCT from the Cochrane review, investigated a psycho-educative intervention part of which involved participants being taught how to manage medicine and tackle problems such as forgetting, delays, side effects and changes in the daily routine. During follow-up participants were provided with skills to deal with minor adverse effects. This study had 116 participants. The mean age in the intervention group was 39 years (s.d=10) and 38 years (s.d=7) in the control group. It appears this study was conducted in Spain. "In an intention to treat (ITT) analysis, no improvements were found in adherence (the p-values were slightly above the 0.05 significance level). However, when a per protocol analysis was conducted, the intervention resulted in improvements in compliance to HAART at 48 weeks. The lack of statistical significance observed using the ITT analysis might be a reflection of a low power to detect differences due to the relatively small sample size for each arm (n=55 for intervention, n=61 for control). The per protocol analysis is suspect in any adherence study as it ignores patients who dropped out, the most severe form of nonadherence." [196].

Peveler (1999) [205], an RCT from the Cochrane review, compared four treatment groups, "…treatment as usual, leaflet, medicine counselling, or both interventions. The information leaflet contained information about the medicine, unwanted side effects, and what to do in the event of a missing dose. Patients were given medicine counselling by a nurse at weeks 2 and 8, according to a written protocol. Sessions included assessment of daily routine and lifestyle, attitudes to treatment, and understanding of the reasons for treatment...The importance of medicine treatment was emphasized, and side effects and their management discussed." [196]. This study had 213 participants with a mean age of 45.3 years with a range of 21-83. This study was conducted in the UK. "The treatment leaflets had no effect on adherence…This study was only 12 weeks in duration, which is shorter than our usual 6 months follow-up criterion. However, because the results were negative for adherence and clinical outcomes with the leaflet intervention, the

paper was included for this review. (Counselling about medicines, however, did result in statistically significant improvements in adherence and clinical outcomes. Nonetheless, because the follow-up was less than six months in duration, the results for counselling are not considered in the conclusions of this review.)" [196].

Howland (1990) [206], an RCT from the Cochrane review, informed intervention group patients of six possible side-effects of treatment with erythromycin, while control (uninformed) patients were not made aware of potential side effects of treatment. This study had 98 participants. The mean age in the intervention group was 50 years and 48 years in the control group. It appears this study was conducted in the USA. The intervention did not increase adherence relative to the control condition nor did it decrease adherence.

8.11.3.3   Adjusting medicine and/or dosage

3 RCTs addressed side effects by giving the intervention deliverer power to adjust medicine and/or medicine dosage.

In a study by **Vivian (2002)** [207] intervention patients saw clinical pharmacists who could make changes in the prescribed medicines and dosages and provided medicine counselling centred around the discussion of side effects, lifestyle and adherence (note we have made an assumption here that the discussion of side effects and changes in medicine are related, this is not explicitly stated in the study). Fifty seven patients aged above 18 years were included in this study. The majority of the study population were African American (77%). There were no statistically significant differences in compliance (from self report measure) between (p>0.25, mean and s.d not given for adherence) or within (p=0.07) the two groups at baseline or at the end of the study. This study was conducted in the USA.

Finley (2003) [208] had pharmacists provide a detailed explanation of the role of antidepressants (including potential therapeutic effects and adverse effects). Care managers were permitted to titrate antidepressant medicines in a fashion consistent with the HMO's clinical guidelines and current

recommended practices (note we have made an assumption here that the discussion of side effects and changes in medicine are related, this is not explicitly stated in the study). During follow-up phone calls and clinic appointments pharmacists followed a standardised set of questions that assessed adverse effects, among other things. One hundred and twenty five patients were included in the study. The majority of the study population was female 42 (84%) in the control group and 64 (85%) in the intervention group; and the mean ages were 54.1 (s.d=17.3) years in the control group and 54.4 (s.d=14.1) years in the intervention group. After 6 months, the intervention group demonstrated a statistically significantly higher medicine adherence rate than that of the control group (67% vs. 48%, p=0.038). This study was conducted in the USA.

As part of a multifaceted intervention, **Katon (2002)** [209] scheduled two sessions for intervention patients with a psychiatrist in a primary care clinic. The study included 228 patients aged between 18 and 80 years. Mean ages were 47.2 (s.d=14) years in the intervention group and 46.7 (s.d 13.4) years in the usual care group. When severe side effects or inadequate response to treatment occurred, the psychiatrist helped the patient and primary care physician alter the dosage or choose an alternative medicine. There were no differences between the four study groups in either adherence to the care suggestions, combined or individually. There were no inter-group differences in medicine adherence. This study was conducted in the USA.

8.11.3.4   Recommendations to health care professionals

2 RCTs addressed side effects by giving the intervention deliverer power to make recommendations to other health care professionals involved in the patients care.

Chisholm (2001) [210] examined an intervention which included a pharmacist taking medicine histories and reviewing medicines with the patient, with an emphasis on optimising medicine therapy to achieve compliance outcomes while minimising adverse events related to medicine. Twenty four patients aged between 18 and 60 years were included in the study. The majority of the

study population was male (75%). The clinical pharmacist also provided recommendations to the nephrologists with the goal of achieving desired outcomes. Counselling involved discussion of patients concerns around their medicine therapy and instructing them how to properly take their medicines. Counselling was both verbal and/or in writing. At 12 months the mean compliance rate in the intervention group was 96.1% (s.d=4.7%) compared to 81.6% (s.d=11.5%) in the control group (p<0.0001). For 6 of the 12 months, higher rates of compliance were seen in the intervention group (p<0.05). Also, 75% (n=9) of the intervention patients were compliant each month compared to 33.3% (n=4) of the control group. This study was conducted in the USA.

Adler (2004) [211] employed a pharmacist intervention which emphasised, among other things: assessing a patient's medicine regimen for medicine-related problems (such as side effects or medicine interactions); monitoring medicine efficacy and toxicity; and educating patients about depression and antidepressants. This study included 533 patients aged above 18 years. The mean age was 42.3 years, and the majority was female. After an initial appointment with the patient, pharmacists provided the patients primary care practitioner with a thorough medicine history (including adherence to prescribed medicines and medicine-related problems) and whatever recommendations the pharmacist may have suggested to improve the regimen. For patients using antidepressants at study entry (n=227) there were no significant differences in antidepressant usage between the intervention and control groups either at 3 (90.7% vs. 87.2, p=0.50) or 6 months (83.4% vs. 78.4%, p=0.33). This study was conducted in the USA.

8.12 How does the way the information is presented (e.g. pictorial vs. written) affect adherence?

Related references	Evidence statements (summary of evidence)
Raynor (2007) [68]	One high quality systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines stated that no robust evidence was found that the information (delivery) had an effect on patient satisfaction or compliance.
Schaffer (2004) [212]	One RCT showed that written information alone and written and verbal information resulted in greater improvements in adherence to prescribed medicine compared to verbal information alone.
Segador (2005) [213]	One RCT showed that verbal and written information compared to verbal information alone resulted in statistically significantly greater improvements in adherence to prescribed medicine.
Atherton-Naji (2001) [214]	One RCT showed that simple tailored information (mailed leaflets with written and pictorial information) did not significantly improve adherence to prescribed medicine compared to usual care.

8.12.1 Evidence to recommendations

For general discussion of limitations of evidence see section 8.3

While there is no conclusive evidence about the effectiveness of the mode of delivery of information affects adherence, in certain cases/diseases it made a difference. The GDG considered from what is know about information provision in other areas that this needs to be individualised to each patient.

8.12.2 Methods of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies - randomised controlled trials (RCTs) of interventions to increase adherence. The excluded studies list from the Cochrane review was checked as we have included those studies with less than 80% follow-up of participants.

Types of participants - people prescribed medicine for a medical condition.

Duration of studies - six months follow up from the time of patient entry for long-term regimens. No time limit specified for short-term conditions.

Types of interventions - any interventions intended to change adherence to prescribed medicine. As the Cochrane review is presented by condition, we have used the evidence extracted in that review and reconfigured it by intervention.

Types of outcome measures - inclusion criteria (as defined in the Cochrane review) were expanded by including studies that used adherence as the only outcome variable as opposed to adherence and treatment outcome variables. The excluded studies list of the Cochrane review was cross-referenced to ensure that no potentially relevant study was missed out.

8.12.3 Evidence review

A health technology assessment report of a "Systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines" [68] was retrieved. This report

aimed to address the role and value of written information given to patients; and how effective this information is in improving patient's knowledge of their treatment and health outcomes. The inclusion criteria of this review was broader than those applied in our reviews, as members of the public not currently taking medicine; general public using over the counter medicines and some addiction therapies were included. Also, studies did not necessarily need to have an aim to increase adherence. Despite these differences, it was felt that due to the high quality of this document, it would be relevant to refer to it in this section to support the evidence included in the reviews and inform the decision making process.

Key findings of the report show that:

- the majority of people do not value the written information they receive, and
- no robust evidence was found that the information had any effect on patient satisfaction or compliance.

Most patients did not value the current package insert patient information leaflets (PILs) and did not consider information written by medicine manufacturers to be sufficiently independent.

The (PILs) supplied had deficiencies in the content (e.g. complexity of language) and layout (e.g. print size). However, it did show that patients valued written information that contained condition-based details along with the medicines information, in addition to alternative treatments for the condition.

In addition, the qualitative evidence included in the report did not show that patients perceive improvement of compliance as a function of PILs. This can be explained by how an informed decision not to take medicine is a legitimate and acceptable outcome. In contrast, some health care professionals viewed that the increase of compliance was one of the main PIL uses.

The key points for improvement of written medicines information outlined by the review were:

- The need to involve patients in all stages of the process, as to reflect better their needs.
- To incorporate the findings from the review to improve future information design and content.
- To present risk information numerically instead of verbal descriptions.

8.12.3.1 *Verbal vs. written vs. verbal and written vs. usual care*

Schaffer (2004) [212], a study from the Cochrane review, compared two interventions and a combination of the two control groups in patients with asthma aged 18-65 (n=46) with results dependant on the measure of adherence used. There were 4 groups, "…standard provider education (control group); (b) audiotape alone; (c) National Heart Lung and Blood Institute (NHLBI) booklet alone; and (d) audiotape plus NHLBI booklet". This study was conducted in the United States.

"The results showed a statistically significant increase in adherence by pharmacy-refill measure (but not by self-report) for NHLBI booklet versus control, and for NHLBI booklet plus audiotape versus control, but not for audiotape versus control at six months".

8.12.3.2 *Verbal and written information vs. verbal information alone*

Segador (2005) [213] compared the effect of written information in addition to verbal information in patients receiving antibiotic treatment for acute sore throat (n = 158) with statistically significant results. Patients in the written information group were given written information at the time of their first visit to their GP. The written information emphasised the importance of completing the antibiotic treatment, of respecting intervals between doses and the drawbacks of an early drop-out, and was given only at the time of initial consultation. The control group was given verbal information only. This study was conducted in Spain.

The pill count average was 87.4 +/- 25.2% and it was higher in the intervention group (93.7 +/- 24.5%) than in the control group (81.1 +/- 24.5%) (p< 0.05).

8.12.3.3 Written and/or pictorial information given vs. usual care

Atherton-Naji (2001) [214] compared an educational intervention to routine care in patients (n=45) with depression with statistically non-significant results. Patients in the intervention group received simple tailored information (mailed leaflets with written and pictorial information) at 1, 6 and 16 weeks after the initial prescription. The leaflets contained basic information about the condition, treatment and general problems people may have with adherence to the treatment. Leaflets were personalised for each patient and their specific medicine. This study was conducted in the UK. Over 6 months, 35.6% (n=16) collected prescriptions at each month (no statistically significant difference between groups). The proportion decreased over time from month 1 (intervention group: 95.8% (n=23) vs. control group: 100% (n=21)) to month 6 (intervention group: 58.3% (n=14) vs. control group: 52.4% (n=11)).

8.13 Do specific forms of therapy (e.g. CBT) affect adherence?

Related references	Evidence statements (summary of evidence)
All studies included in evidence review	There is some evidence that elements of CBT or psycho-behavioural can help but the quality of the evidence does not allow us to generalise these results.
Gray 2006 [215]; Wyatt 2004 [216]; Bechdolf 2004 and 2005 [217] [218]; Weber 2004 [219]; Antoni, 2006 [220]; Wagner 2006 [221]; Lam, 2003 [222]	The majority of evidence suggests that CBT approaches do not improve adherence relative to other forms of treatment.
Strang (1981) [223]	One RCT showed that family therapy increased adherence to prescribed medicine when compared to individual support sessions.
Xiong (1994) [224]; Zhang (1994) [225]	Two RCTs showed that family therapy did not increase adherence to prescribed medicine when compared to standard care.
Miklowitz, 2003 [226]	One RCT showed that family therapy and pharmacotherapy increased adherence to prescribed medicine when compared to crisis management and pharmacotherapy.
Razali, 2000 [227]	One RCT showed that culturally modified family therapy increases adherence when compared to behavioural family therapy.
Remien, 2005 [228]	One RCT showed that couple based therapy

	increases adherence compared to usual care.
Ruskin, 2004 [229]	One RCT showed that telepsychiatry did not increase adherence compared to face to face psychiatry.
Kemp 1996, 1998 [230] [200]; O'Donnell 2003 [231]	There is conflicting evidence with regards to whether compliance therapy increases adherence compared to counselling.
Pradier, 2003 [232]; Van Servellen (2005) [233]	There is conflicting evidence to suggest that multi-component interventions mainly based on motivational principles increase adherence.
Weber 2004 [219]	One RCT showed that CBT and usual care did not increase adherence compared to usual care alone.
Gray, 2006 [215]	One RCT showed that CBT and health education did not increase adherence compared to health education alone.
Bechdolf, 2004 and 2005 [217] [218]	One RCT showed that CBT and health education did not increase adherence compared to psycho-education.
Antoni 2006 [220]	One RCT showed that cognitive behavioural stress management in addition to antiretroviral medicine adherence training did not increase adherence compared to medicines adherence training alone.

8.13.1 Evidence to recommendations

For general discussion of limitations of evidence see section 8.3

The evidence concerning specific forms of therapy and their effect on adherence is inadequate. Conclusions from a variety of single studies with ill defined content and delivery are inconclusive. The GDG noted that definitions of CBT and other therapies were often unclear. It was also argued that some of these interventions may not be salient to medicine-taking behaviour. The available evidence is that patients make their own appraisal of medicines based on factors important to them and in this context their behaviour is rational and coherent and as such not appropriate for CBT.

Therapies which worked with patients and families addressing social and cultural issues do provide evidence of specific principles of engaging with patients that may be of value. The evidence for CBT/other forms of therapy comes from patients with severe mental illness and HIV. Evidence from these populations might not be generalised to other medicine-taking populations.

8.13.2 Methods of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies - randomised controlled trials (RCTs) of interventions to increase adherence. The excluded studies list from the Cochrane review was checked as we have included those studies with less than 80% follow-up of participants.

Types of participants - people prescribed medicine for a medical condition.

Duration of studies - six months follow-up from the time of patient entry for long-term regimens. No time limit specified for short-term conditions.

Types of interventions - any interventions intended to change adherence to prescribed medicine. As the Cochrane review is presented by condition, we have used the evidence extracted in that review and reconfigured it by intervention.

Types of outcome measures – inclusion criteria (as defined in the Cochrane review) were expanded by including studies that used adherence as the only outcome variable as opposed to adherence and treatment outcome variables. The excluded studies list of the Cochrane review was cross-referenced to ensure that no potentially relevant study was missed out.

8.13.3 Evidence review

8.13.3.1 Family Therapy

Miklowitz (2003) [226] compared family focused therapy and pharmacotherapy with crisis management and pharmacotherapy (serving as control group) in patients with bi-polar disorder with positive results. The study included 101 participants with ages that ranged from 18 to 62 years (mean age 35.6 ± 10.2 years). Family focused therapy involved three modules: 1/ psycho-education, which involved passing on information about the disorder, its aetiology, signs, symptoms and also information on how to prevent relapse; 2/ communication training where, through role play, skills of listening, offering feedback, and requesting changes in behaviour were passed on; and 3/ problem solving skills, where participants identified potential problems, came up with and evaluated various solutions. Family focused therapy involved approximately 21 sessions over a nine month period and was conducted with the whole of the patient's family at the patients/family's home. This study was conducted in the USA.

Patients in the intervention group had higher mean medicine adherence scores during follow up (2.77 +/- 0.43) than patients in the control group (2.56 +/- 0.48, p=0.04). This study was conducted in the USA.

Razali (2000) [227], a RCT from the Cochrane review, compared the effects of "culturally modified family therapy"(CMFT) to the effects of "behavioural family therapy" (BFT serving as the control condition) in patients with schizophrenia. This study included 166 participants, with ages ranging from 17 to 55 years. The majority of the patients came from a low socio-economic background. The CMFT was delivered by a psychiatrist and sessions were given monthly for the first 3 months and then every 6 weeks in the following months. The

CMFT consisted of a "….Socio-cultural approach of family education, medicine intervention programme and problem-solving skills. The socio-cultural approaches to family education include explanations of the concept of schizophrenia from a cultural perspective and an attempt to correct negative attitudes toward modern treatment. The family education and medicine intervention was delivered as a package. The medicine intervention programme included medicine counselling, clear instruction about dose, frequency and possible side effects, the role of carers in supervision of medicine-taking at home, and close monitoring of compliance by a medicine intake check-list presented in every follow-up visit [196]." This study was conducted in Malaysia.

At six months there was no significant difference in compliance but at 1 year the intervention (CMFT) group had statistically significantly higher compliance than those in the control (BFT) group. Ninety percent compliance was achieved by 85% of the CMFT group and 55% of the BFT group, p<0.001.

Strang (1981) [223], a RCT from the Cochrane review, compared family therapy or individual support sessions in patients with schizophrenia with positive results. Thirty two patients were enrolled in this study. No information on the ages of the patients was given. All patients had scheduled therapy and monthly medicine appointments. Patients were allocated to family therapy or individual support sessions. This study was conducted in the UK.

The patients in the family therapy group were statistically significantly more adherent than those in the individual support group.

Xiong (1994) [224], a study from the Cochrane review, compared a family based intervention with standard care in patients with schizophrenia with negative results. Sixty three families were enrolled in this study and mean age was 31 years (ranging from 17 to 54 years). The family based intervention "…included monthly 45 minute counselling sessions focused on the management of social and occupational problems, medicine management, family education, family group meetings, and crisis intervention" [196]. This study was conducted in

China. There was no difference in terms of adherence between the two groups.

Zhang (1994) [225], a study from the Cochrane review, compared a family intervention with no additional care above standard care in patients discharged after their first admission to the hospital for schizophrenia with negative results. This study included 83 patients. Mean ages were 23.5 (sd=7.6) for the intervention group and 24.1 (sd=8.1) for the control group Families and patients in the family intervention group were "…assigned to one of two counsellors for their ongoing care, were invited to come to a discharge session that focused on education about the management of the patient's treatment, asked to come to a family group counselling session with other families three months after discharge, and then attend three-monthly group sessions with other families with similar patient problems. Non-attendance triggered a visit from study staff. Each family was contacted at least once during the 18-month follow-up." [196] This study was conducted in China. There was no difference in terms of adherence between the two groups.

8.13.3.2 Couples Therapy

Remien (2005) [228] compared a couple-based ART adherence intervention with usual care in HIV-serodiscordant couples with positive results. The intervention included structured discussions and instruction, as well as specific problem-solving and couple-communication exercises. A total of 215 couples aged >18 years were enrolled in the study. The mean age of the participants was 42 years. The study sample mainly consisted of lower-income racial/ethnic minorities. Key components included education about the importance of adherence to avoid viral resistance and maintain health, identifying patterns of nonadherence, developing communication and problem-solving strategies to overcome adherence barriers, optimising partner support and building confidence in the couple for achieving and maintaining improved adherence. In addition the intervention sought to help couples to address issues of sex and intimacy. The intervention was administered to each couple by a nurse practitioner through 45-60 min sessions held over 5 weeks. The study was conducted in the USA.

At 6 months there were statistically significant differences in adherence change between the 2 groups.

Statistically significant group differences in adherence change from baseline to week 8 in terms of proportion of prescribed doses taken (p=0.021) and proportion of doses taken within specified windows (p<0.001). At 3 months only the proportion of doses taken within specified time windows was statistically significant (p=0.028).

8.13.3.3 Telepsychiatry

Ruskin (2004) [229] compared patients being seen by a psychiatrist, either in person or by means of telepsychiatry, who had one of the following five diagnoses: major depressive disorder, dysthymic disorder, adjustment disorder with depressed mood, mood disorder due to a general medical condition, or depressive disorder not otherwise specified with negative results. One hundred and thirty one patients were enrolled in the study. Mean age of participants was 49.7 (sd=12.8) years. Treatment sessions lasted approximately 20 minutes and consisted of antidepressant medicine management, psycho-education, and brief supportive counselling. Treatment consisted of eight sessions with a psychiatrist over a 6-month period. This study was conducted in the USA.

There was no difference in the percentage of adherent patients between the two treatment groups.

8.13.3.4 Compliance Therapy

Kemp's (1996, 1998) [230] [200] RCTs from the Cochrane review, compared "compliance therapy" with supportive counselling sessions (serving as the control group) in patients with psychotic disorders with statistically significant results. Forty-seven patients aged 18 to 65 years were included in the 1996 study and 74 patients also aged 18 to 65 years in the 1998 study. Compliance therapy consisted of 4 to 6 sessions and was defined as, "…a strategy that borrows from motivational interviewing. During session 1 and session 2, patients reviewed their illness and conceptualized the problem. In the next 2 sessions, patients focused on symptoms and the side effects of treatment. In

the last 2 sessions, the stigma of medicine-taking was addressed [196]". This study was conducted in the UK.

At 12 months patients receiving compliance therapy received higher adherence ratings (p< 0.001) than those patients receiving non-specific counselling.

O'Donnell (2003) [231], a RCT from the Cochrane review compared "compliance therapy" with non-specific counselling (as the control group) in patients with schizophrenia, with negative results. The study included 94 patients aged between 18 and 65 years. The mean age for both of the groups was 32 years (s.d=9). The intervention lasted 5 sessions, each session lasting 30-60 minutes. It is reported that, "…the sessions covered a review of the patient's illness history, understanding of the illness and his or her ambivalence to treatment, maintenance medicine and stigma. Compliance therapy is a cognitive behavioural intervention with techniques adapted from motivational interviewing, other cognitive therapies and psycho-education." [196]. This study was conducted in Ireland.

There was no difference in terms of adherence between the two groups.

8.13.3.5   Multicomponent intervention

Pradier (2003) [232], a RCT from the Cochrane review, compared a combined educational and counselling intervention with a control condition in patients with HIV with positive results. The study included 244 patients aged >18 years. Median age of the participants was 40 years in the intervention group and 38 years in the control group. The intervention consisted of 3 individual sessions delivered by nurses lasting 45-60 minutes. The intervention was, "…founded on the principles of motivational psychology, client centred therapy and the use of an "empathic therapeutic to enhance participants' self efficacy". The intervention focused on cognitive, emotional, social and behavioural determinants affecting adherence." [196] This study was conducted in France.

Self-reported adherence between baseline and six months was statistically significantly improved in the intervention group, versus control. 75% of the

intervention group and 61% of the control group reported adherence at 6 months (p=0.04). Compared to 58% vs 63% at baseline (p=0.59).

Van Servellen (2005) [233] compared an enhanced adherence intervention with standard clinical care in patients (n = 85) taking antiretroviral medicines for at least 3 months with negative results. To be eligible to take part in this study participants must be able to speak Spanish. The enhanced adherence intervention consisted of two parts the first being modular instruction which was aimed at increasing patients HIV knowledge and ability to communicate with medical staff and was delivered over 5 sessions by health educators and nurses. These were followed up by case management sessions, delivered either face to face or via a telephone by a nurse, which concentrated on addressing the patient's potential or actual risks for nonadherence using motivational interviewing techniques. Content involved going over things misunderstood in the modular instruction stage, identifying barriers to adherence and finding strategies to challenge these and helping to find community, treatment and social support/referrals to help address adherence barriers. This study was conducted in the USA. There were no statistically significant differences between the group at 6 months.

8.13.3.6   Cognitive Behavioural Treatment

Antoni (2006) [220] compared cognitive behavioural stress management (CSBM) in addition to antiretroviral medicine adherence training (MAT) with MAT alone in patients with HIV with negative results. CSBM sessions included a didactic component, as well as group discussion, with opportunities provided to apply newly learned techniques. One hundred and thirty patients aged between 18 and 65 years were included in the study. The mean age was 41.6 (s.d=8.3) years. Homework was assigned to provide opportunities for participants to practice techniques and increase their self-efficacy. The treatment was focused extensively on eliciting participant experiences with adherence and medicine side effects. Throughout the 10-week, 135-minute group sessions (90 minute stress management and 45 minute relaxation), facilitators encouraged participants to examine potentially distorted cognitions and how these may influence adherence to HAART (as well as other relevant

self-care behaviours). During cognitive restructuring exercises, participants were asked to examine medicine-relevant thoughts both in session and through homework exercises. Adherence was also a key target during the skills training sessions. This study appears to have been conducted in the USA (not explicitly stated).

The experimental conditions did not differ statistically significantly in participant-reported medicine adherence throughout the 15-month investigation period.

Bechdolf (2004 and 2005) [217] [218] compared group CBT with group psycho-education (PE) in patients who had suffered an episode of a schizophrenia or a related disorder with negative results. Eighty-eight patients aged between 18 and 64 years were included in the study. Only a minority of patients were employed. Group CBT focused on assessment and engagement (sharing information about voices and delusions, models of psychosis), improving self-esteem, formulation of key-problems and developing interventions directed at reducing the severity and the occurrence of key problems, relapse prevention/keeping well and enhancing medicine compliance. There was a specific focus on the component "improving self-esteem" to foster feelings of hope and engagement with therapy. Group CBT involved 16 sessions in 8 weeks by a psychiatrist or clinical psychologist. This study was conducted in Germany.

Compliance was high initially (group CBT mean: 3.9 (s.d=0.3) vs. PE group: 3.8 (s.d=0.5)). At 8 weeks post-treatment, there was no statistically significant difference between groups (3.9 (s.d=0.3) vs. 3.7 (s.d=0.7)) nor at 6 months (3.5 (s.d=0.9) vs. 3.2 (s.d=1.0). This remained statistically non-significant when corrected for pre-treatment scores. At 24 month follow-up again no statistically significant differences were seen (3.4 (s.d=0.7) vs. 2.9 (s.d=1.1).

Weber (2004) [219], a RCT from the Cochrane review, compared cognitive behavioural therapy in addition to usual care to usual care alone in patients with HIV with negative results. The study included 60 patients, and the median age was 41 years. The intervention was delivered by a

psychotherapist. The Cochrane Review informs that, "…protocol defined a minimum of three and a maximum of 25 sessions within the one year study period. The participant and psychotherapist determined the frequency of appointments and set their own goals for future interventions. The intervention had to be based on concepts of cognitive behavioral therapy" [196]. This study was conducted in Switzerland.

There was no statistically significant difference in mean adherence between the two groups, but both groups had very high mean adherence rates (92.8% versus 88.9%), and a higher proportion of intervention group patients were at or above 95% adherence (70% versus 50%, p=0.014).

There was no difference in terms of adherence between the two groups.

Lam (2003) [222] compared cognitive therapy and minimal psychiatric care v minimal psychiatric care alone in patients with bi-polar disorder with positive results. One hundred and three patients with ages ranging from 18 to 70 years were enrolled in the study. Mean age was 46.4 (sd=12.1) years for the intervention group and 41.5 (sd=10.8) for the control group. Traditional cognitive therapy for depression was provided by clinical psychologists with new elements highlighting the need for combined psychological and medicine treatment, CBT skills for monitoring mood and preventing relapse and highlighting the importance of sleep and routine. The therapy also addressed illness beliefs. Cognitive therapy involved 12 to 18 individual sessions within the first 6 months and 2 booster sessions in the second 6 months. This study was conducted in the UK.

At 14 months, medicine adherence was 95.5% (sd=7.7%) in the cognitive therapy group and 69.1% (sd=16.4%) in the control group (p<0.001). Proportions of people who had at least 80% adherence rates were 97.4% in the cognitive therapy group and 21.7% in the control group (p< 0.001).

Gray (2006) [215] compared adherence therapy (AT) with health education (HE) (serving as the control group) in patients with schizophrenia with negative results. Adherence therapy is a brief, individual CBT approach. Six elements formed the core of the therapy: assessment, medicine problem solving,

medicine timeline, exploring ambivalence, discussing beliefs and concerns about medicine and using medicine in the future. Three hundred patients were included in the study, and the mean age was 41.5 (s.d=11.5) years. Key therapy skills that the therapists use included exchanging information, developing discrepancies between participant's thoughts and behaviours about medicines and working with resistance to discussing psychiatric medicine and treatment. The overall aim of process was to achieve a joint decision about the medicine. Participants were offered a maximum of 8 sessions lasting 30-50 minutes over a 5 month period and the intervention was delivered by 9 therapists (four psychologists, three psychiatrists and 2 mental health nurses). The study was conducted in 4 countries: The Netherlands, Germany, England and Italy.

At 12 months, there were no statistically significant differences between the groups using either patient assessment (AT group: 3.20 (s.d=1.07), HE group: 3.33 (s.d=1.02), 95% CI -0.35 to 0.08) or clinical assessment (AT group: 5.22 (s.d=1.57) HE group: 5.03 (s.d=1.55), 95% CI -0.12 to 0.52) of adherence.

Wagner (2006) [221] compared a cognitive behavioural treatment with an enhanced condition of the treatment (a 2 week pre-treatment practice trial) and a control group, for the effect on adherence to a new regime of antiretroviral therapy. The study included 230 patients with a mean age of 39 (ranging from 21 to 70 years), 80% were male, 49% were Latino(a) and 65% were unemployed. The study was set in the USA. The intervention involved five sessions of cognitive behavioural therapy. Questionnaires were administered and blood was drawn at screening (four weeks before treatment baseline), and periodically up to 48 weeks from the start of treatment. There was no difference in adherence between the intervention and the enhanced intervention group. There was initially a statistically significant increase in attaining 'good' adherence (90% of prescribed dose) for the intervention groups compared to the control group (82% versus 65%, p=0.01). The difference reduced in the following weeks and was not statistically significant. At week 48 the difference was reversed to 57% (intervention group) versus 65% (control group), but this was also statistically non-significant (p=0.52).

Wyatt (2004) [216] compared a cognitive behavioural approach (the Enhanced Sexual Health Intervention) to usual care for risk reduction and treatment adherence for 147 women who had HIV and a history of childhood sexual abuse. The mean age was 41 (s.d=8.2), 25-65 years, 51% were African American and 49% were Latina and primarily unemployed. The study was set in the USA. The intervention involved 11 weekly sessions for 2.5 hours per week of psycho-educational content relating to child sexual abuse and HIV status. They were followed up at the end of the 11 weeks and then again at 3 and 6 months. Although an effect was found for risk reduction there was no increase in adherence to medicine in the intervention group (75.6% versus 73.3%, OR=1.13, p=0.41). However a statistically significant effect was found for adherence for those who attended at least eight sessions (91.3%) compared to seven or fewer (49.7%), OR=4.90, p=0.044. The difference in adherence of the high attendees was 91.3% compared to the control group was 74.7%, this was statistically significant.

8.14   Would a contractual agreement between HCP and patient affect adherence?

Related references	Evidence statements (summary of evidence)
Bosch-Capblanch (2007) [234]	Evidence from one high quality systematic review of RCTs suggests that the use of contracts within a healthcare setting does not appear to increase adherence to prescribed medicine. These RCTs included hypertension (2 RCTs), acne, acute bacterial infection, asthma, depression, diabetes and tuberculosis. Only one RCT, for hypertension, and one RCT for acute bacterial infection, showed a statistically significant increase in adherence.

8.14.1 Evidence to recommendations

For general discussion of limitations of evidence see section 8.3.

It should be noted that patients with substance abuse issues are considered to fall outside the scope of this guideline and therefore are not included in this evidence review.

There is no evidence to show that contractual arrangements have any impact in improving adherence and the GDG did not wish to make a recommendation in this area.

8.14.2 Methods of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies - Randomised controlled trials (RCTs) of interventions to increase adherence. The excluded studies list from the Cochrane review was checked as we have included those studies with less than 80% follow-up of participants.

Types of participants - people prescribed medicine for a medical condition.

Duration of studies - six months follow-up from the time of patient entry for long-term regimens. No time limit specified for short-term conditions.

Types of interventions - any interventions intended to change adherence to prescribed medicine. As the Cochrane review is presented by condition, we have used the evidence extracted in that review and reconfigured it by intervention.

Types of outcome measures - inclusion criteria (as defined in the Cochrane review) were expanded by including studies that used adherence as the only outcome variable as opposed to adherence and treatment outcome variables. The excluded studies list of the Cochrane review was cross-referenced to ensure that no potentially relevant study was missed out.

8.14.3 Definitions of contracts

Contracts can be generically viewed as reciprocal agreements between two or more parties in which one or more will need to do something.

From a behavioural strategy perspective, a contract to increase patient's adherence can be defined as "a process of specifying a set of rules regarding some behaviour of interest and formalising a commitment to adhere to them" [21].

Contracts can be written or verbal. Most contracts are between healthcare practitioners and patients, but they may also occur between practitioners and carers, carers and patients or by a patient with him/herself.

8.14.4 Evidence review

We retrieved one Cochrane review that aimed to assess whether contracts between healthcare practitioners and patients had an effect on patients' adherence to treatment, prevention and health promotion activities Bosch-Capblanch (2007) [234]. Although this review included settings other than clinical settings, we decided to include this high quality systematic review of RCTs on the grounds that the results were reported in groups, thus allowing us to make conclusions from those settings relevant to the guideline. It also included other treatment groups that are outside the remit of the guideline, such as substance addiction treatments and interventions for hypertension and overweight without prescribed medicine. Other areas that were included were acne, acute bacterial infections, arthritis, asthma, breast self examination, contact lens care, depression, diabetes, phobias, promotion of healthy diet and exercise and tuberculosis.

The Cochrane review also assessed the effects of contracts on other outcomes, including patient participation and satisfaction, health practitioner behaviour and views, health status, harms, costs, and ethical issues.

Seven trials assessed contracts between HCPs and patients, nine trials assessed contracts between patients and carers, peers or others, and between HCPs and carers in one trial. Four trials assessed contracts between HCPs, patients and carers, two trials assessed self-contract and the other seven trials did not report which type of contract was being used. Twenty one trials included some type of financial incentive.

Several of the trials were of poor quality and included small numbers of people. Most were conducted in the USA and were conducted in specialised services.

Two trials that examined the effects of contracts in the context of hypertension management reported adherence outcomes. However, only one showed statistically significant results in favour of the group with contracts.

In the miscellaneous section, six trials in the contexts of acne, acute bacterial infection, asthma, depression, diabetes and tuberculosis reported adherence outcomes. However, in some cases it was not possible to determine whether adherence was also related to prescribed medicine or with an overall treatment regime (depression, and diabetes). From these, five trials did not report any statistical significance in favour of the contracts groups, whilst the acute bacterial infection trial reported statistically significantly better results (based on pill count) in the contract group. However, there was no difference between groups in self-reported adherence, nor in the number of additional prescriptions to finalise the treatment.

Based on the results for the trials that included an assessment of patients' adherence to medicine, the use of contracts does not appear to improve adherence.

Overall, the conclusions from the Cochrane authors state that there is limited evidence that contracts can have a positive effect in improving adherence. In addition they argue that there is insufficient evidence from large, good quality studies to routinely recommend contracts for improving adherence to treatment or preventive health regimens [234].

8.15 Does being involved in self-monitoring (e.g. of own blood pressure) increase adherence to prescribed medicine?

Related references	Evidence statements (summary of evidence)
Haynes (1976) [235]; Sadik (2005) [236]; Tsuyuki (2004) [237]	The majority of evidence suggests that involving patients in the self-monitoring of their medicine adherence (e.g. through recording adherence in diary logs) appears to increase adherence as part of a multi-component intervention.
Sadik (2005) [236]; Bailey (1990) [238]; Cote (1997) [239]; Cote (2001) [240]; Friedman (1996) [241]; Haynes (1976) [235]; Johnson (1978) [242]; Morice (2001)[243]; Peterson (1984) [185]	There is conflicting evidence in regard to whether having patients record information (e.g. in a diary log) relevant to their condition (e.g. symptoms) can increase adherence as part of a multi-component intervention.
Haynes (1976) [235]; Cote (1997) [239]; Morice (2001) [243]; Bailey (1990) [238]; Bailey (1999) [244]; Cote, (2001) [245].	There is conflicting evidence with regard to whether providing participants with information on how to adjust their treatment based on their own self-monitoring affects adherence.
Morice (2001) [243]; Cote (1997) [239]; Bailey (1990) [238]; Cote (2001) [245]; Levy (2000) [246]	There is conflicting evidence that involving patients more in their care through the self-monitoring of respiratory function through measurement of PEF increases adherence as part of a multi-component intervention.
Friedman (1996) [241]; Haynes (1979) [235]; Johnson (1978) [242]; Marquez-Contreras (2006) [247]; Rudd	There is conflicting evidence with regard to whether involving patients in the self-monitoring of their blood pressure improves adherence as part of a multi-component intervention.

(2004 [175]	

8.15.1 Evidence to recommendations

For general discussion of limitations of evidence see section 8.3

The evidence of the value of self-monitoring in increasing adherence was conflicting. The GDG considered that this was perhaps not surprising given that qualitative evidence had indicated that patients may use such measures to inform their own decisions and evaluations of treatments rather than to ensure they follow a previous decision. Self-monitoring is also used in conditions where the patient can alter treatment according to results and this group will have different characteristics and needs than a general patient group.

8.15.2 Methods of the evidence review

This paper includes a narrative summary of the included evidence, structured according to the category of the intervention, following the agreed reviewing protocol:

Types of studies - randomised controlled trials (RCTs) of interventions to increase adherence. The excluded studies list from the Cochrane review was checked as we have included those studies with less than 80% follow-up of participants.

Types of participants - people prescribed medicine for a medical condition.

Duration of studies - six months follow-up from the time of patient entry for long-term regimens. No time limit specified for short-term conditions.

Types of interventions - any interventions intended to change adherence to prescribed medicine. As the Cochrane review is presented by condition, we have used the evidence extracted in that review and reconfigured it by intervention.

Types of outcome measures – inclusion criterion (as defined in the Cochrane review) was expanded by including studies that used adherence as

the only outcome variable as opposed to adherence and treatment outcome variables. The excluded studies list of the Cochrane review was cross-referenced to ensure that no potentially relevant study was missed out.

8.15.3 Evidence review

Although a handful of studies were found which addressed self monitoring we did not find any study where the study interventions sole purpose was to address self monitoring (although arguably a few appear in the Cochrane review studies). Within the studies which did address self monitoring there was variability in how they did this and to what extent self monitoring was a focus of the intervention. Narratives of each study, which give full details of the entire intervention used in each individual study, are summarised below.

Tsuyuki (2004) [237] compared a patient support program with usual care in patients with heart failure with negative results. Seven hundred and sixty six patients aged above 18 years were enrolled in the study. The mean age of the patients was 74 years. Patients in the support group received educational material consisting of information about heart failure, non-drug treatment, medicine information (with special emphasis on proven benefits of therapies) and self-monitoring, all written at a grade 8 reading level. Patients also received adherence aids including a medicine organiser, medicine administration schedule, and daily weight log. Community follow-up in the patient support program consisted of telephone contact by the local research coordinator at 2 and 4 weeks and then monthly there after for 6 months after discharge. The telephone contact was to reinforce education and adherence relating to heart failure and other self-care activities, focusing on the 5 essential components: salt and fluid restriction, daily weighting, exercise alternating with rest periods, proper medicine use and knowing when to call their physician. This study was conducted in Canada. ACE inhibitor adherence over 6 months after discharge was 86.2 ± 29% in the usual care group vs. 83.5 ± 29% in the patient support group (p= ns).

Sadik (2005) [236] compared a pharmacist-delivered intervention with usual care in patients with heart failure with positive results. A total of 221 patients were enrolled in the study. Mean age of participants was 58 years. For the

Medicines Adherence: Full Guideline (January 2009) Page 280 of 364

intervention group patients the research pharmacist discussed with their physicians if rationalisation of medicine therapy or simplification of dosage regimens were considered appropriate. Intervention patients were also educated (in a structured fashion) on heart failure, their prescribed medicine and the management of heart failure symptoms by the research pharmacist. A printed booklet developed for this type of education programme was used and each patient was given a copy to take home. The booklet contained information on heart failure, its symptoms, the aims of treatment, the types of medicine used and their possible side-effects, diet and lifestyle changes, advice to stick to one brand of digoxin (it having a narrow therapeutic index) and information on the action to take if doses of medicine were missed. Intervention group patients were also instructed on a self-monitoring programme (signs and symptoms of heart failure; compliance with prescribed medicine) in which they were asked to become involved; a monitoring diary card (covering 1 month) was used. Patients were asked to complete their monitoring diary cards at home and to show them to their physicians when attending an appointment. The patients were asked to return their completed diary cards to the research pharmacist for review when they visited the hospital to receive medicine refills. Reinforcement of the educational message was carried out by the pharmacist as deemed necessary. This study was conducted in the United Arab Emirates.

The number of intervention group patients vs. control patients who exhibited self-reported compliance with the prescribed medicines (85 vs. 35) and lifestyle adjustment (75 vs. 29) was higher than in control group patients at 12 months (p<0.05).

Bailey (1990) [238], a study from the Cochrane review, compared a multi-faceted intervention with standard care in patients with recurrent episodes of wheezing with positive results. A total of 267 patients aged above 18 years were enrolled in the study. Patients in the intervention group were, "…provided with the standardised asthma pamphlets and were provided with a skill-oriented self-help workbook, a one-to-one counselling session, and were subject to several adherence-enhancing strategies, such as attending an

asthma support group and receiving telephone calls from a health educator. Physicians emphasised these skills at regular clinic visits." [196] The Cochrane review also states that the intervention included involving patients more in their care through self-monitoring of their respiratory function. This study was conducted in the USA. The intervention group were statistically significantly more adherent than the control group.

Bailey (1999) [244], a study from the Cochrane review, conducted a randomised controlled trial of asthma self-management. 236 patients stratified by moderate or severe asthma in Alabama, USA, were randomised to the University of Alabama Birmingham (UAB) asthma self-management group, the UAB core-elements group and usual care group. The core components involved a skill-oriented self-help asthma workbook, which the patients were counselled in for one hour. The participants also received 2 telephone calls and a letter at 1, 2 and 4 weeks to discuss problems and peak flow readings (see Bailey 1990). The core elements program involved a shorter version of the workbook of which counselling was given briefly (15-20 minutes). They were trained to use inhalers and peak flow meters. Participants were followed up by telephone a week later and a letter 2 weeks later. The usual care group received usual education from their GP and informational leaflets. There were no statistically significant differences between groups in adherence.

Cote (1997) [239], a study from the Cochrane review, compared two intervention groups and one control group in patients with moderate to severe asthma with negative results. A total of 188 patients aged above 16 years were enrolled in the study. The intervention was an "…asthma education program with an action plan based on peak-flow monitoring (Group P) or an action plan based on asthma symptoms (Group S). The control group (Group C) received instructions from their pulmonologists regarding medicine use and influence of allergenic and non-allergenic triggers. They were taught how to use their inhaler properly by the educator. A verbal action plan could be given by the physician. Groups P and S received the same education as the controls plus individual counselling with the specialised educator during a 1-hour session. All participants received a book titled "Understand and Control Your Asthma"

at no extra charge. Group P received a self-management plan based on peak expiratory flow (PEF). They were asked to continue measuring PEF twice a day and to keep a diary of the results. Each time, subjects only recorded the best of three measurements. Every attempt was made to ensure that patients knew how to interpret the measurement and how to respond to a change in PEF. At each follow-up visit, the patient's diary card was reviewed, and if the action plan had not been implemented when required, further explanations were given regarding when treatment should be modified. Group S received a self-management plan based on asthma symptom monitoring. These patients were asked to keep a daily diary of asthma symptom scores, using a scale of 0 (no symptoms) to 3 (night time asthma symptoms, severe daily symptoms preventing usual activities), and adjust their medicines according to the severity of respiratory symptoms using the guidelines of the action plan." [196] This study was conducted in Canada. Neither intervention had a statistically significant effect on participants' adherence.

Cote (2001) [245], a study from the Cochrane review, compared two different educational interventions with usual care for adult patients consulting with an acute asthma exacerbation with negative results. A total of 126 patients aged above 18 years entered the study. Patients in the Limited Education (LE) group were given a self-action plan that was explained by the on-call physician. The action plan used "traffic lights" (green, yellow, red) to describe specific states of asthma control based on Peak Expiratory Flow and symptoms and actions that the patient should take for each state. Patients in a "Structured Educational group (SE)", in addition to what patients in Group LE received, participated in a structured asthma educational program based on the PRECEDE model of health education. This model took into consideration three different issues that were important when dealing with health-related behaviours: predisposing factors (belief, attitude, knowledge), enabling factors (community resource, family support), and reinforcement. Reinforcement was provided at the 6-month follow-up visit and the teaching was provided individually or in small groups according to patient preference. Both intervention groups also received usual care." [196] This study was conducted in Canada.

Neither intervention had a statistically significant effect on participants' adherence.

Levy (2000) [246] compared a nurse-delivered intervention with usual care in patients with asthma (n=211) with positive results. The intervention group were, "…invited to attend a 1h consultation with one of the nurses beginning 2 weeks after entry to the study, followed by two or more lasting half an hour, at 6-weekly intervals. The second and third could be substituted by a telephone call. Patients were phoned, by the nurse before each appointment in order to improve attendance rates. Patient's asthma control and management were assessed followed by education on recognition and self-treatment of episodes of asthma. The patients were taught to step-up medicine when they recognised uncontrolled asthma using PEF or symptoms. The advice was in accordance with national guideline. Prescriptions were obtained from one of the doctors in the clinic or by providing the patient with a letter to their general practitioner. Patients presenting with severe asthma (severe symptoms of PEF below 60% of their best/normal) were referred immediately to the consultant." [196] This study was conducted in the UK

Self-reported compliance was statistically significantly higher in the intervention group for use of inhaled topical steroids and rescue medicine for severe asthmatic attacks, but there was no statistically significant difference between the groups for use of these medicines for mild attacks.

Friedman (1996) [241], a study from the Cochrane review, compared a telephone-linked computer system (TLC) intervention for monitoring and counselling patients with usual care in patients with hypertension with positive results. Two hundred and sixty seven patients aged ≥ 60 years were recruited for the study. The mean age was 76 years for the TLC group and 77 years for the usual care group. TLC is, "…an interactive computer-based telecommunications system that converses with patients in their homes, using computer-controlled speech, between office visits to their physicians. The intervention patients would call the TLC on a weekly basis. Before calling, subjects would record their own blood pressure using an automated sphygmomanometer with a digital readout. During the conversation, subjects

would answer a standard series of questions and the TLC would provide education and motivational counselling to improve medicine adherence. The TLC then transmitted the reported information to the subject's physician". [196] This study appears to have been conducted in the USA.

The unadjusted results did not demonstrate a statistically significant improvement in compliance or clinical outcome in patients using TLC as compared to those patients receiving usual care. However, when the data were adjusted for age, sex, and baseline adherence, the patients using TLC demonstrated a greater improvement in medicine adherence than those receiving usual care (p<0.05). Sub-group analysis showed, in people who were nonadherent at baseline, patients using TLC had greater improvement in medicine compliance (p<0.05) than those receiving usual care. In people who were adherent at baseline, TLC showed no statistically significant difference in adherence between the two groups over the course of the trial.

Haynes (1976) [235], a study from the Cochrane review, compared a multi-component intervention with usual care in patients with high blood pressure with positive results. Thirty nine patients were enrolled in the study. It is not clear from the study the ages of the patients. Patients in the intervention group were, "…all taught the correct method to measure their own blood pressures, were asked to chart their home blood pressures and pill taking, and taught how to tailor pill-taking to their daily habits and rituals. They also visited fortnightly (at the worksite) a high-school graduate with no formal health professional training who reinforced the experimental manoeuvres and rewarded improvements in adherence and blood pressure. Rewards included allowing participants to earn credit, for improvements in adherence and blood pressure, which could be applied towards the eventual purchase of the blood pressure apparatus they had been loaned for the trial". [196] This study was conducted in Canada. There was a statistically significant increase in adherence associated with the intervention.

Johnson (1978) [242], a study from the Cochrane review, compared four groups (1) self-recording and monthly home visits, (2) self recording only, (3) monthly home visits, and a control group consisted of (4) neither self-recording nor

home visits with negative results. One hundred and forty patients aged between 35 and 65 years were included in the study. Patients receiving antihypertensive medicines were studied. Participants, "…in groups (1) and (2) received a blood pressure kit and instruction in self-recording. Patients in the self-recording groups were to keep charts of their daily blood pressure readings and were instructed to bring these charts to their physician at each appointment. Subjects in groups (1) and (3) had their blood pressure measured in their homes every four weeks, and the results were reported to both the patient and the physician" [196]. This study was conducted in Canada. There was no effect on adherence from either intervention.

Marquez-Contreras (2006) [247], included in the Cochrane updated review, conducted a randomised controlled trial of a programme of home blood pressure management (HBPM) in patients with mild-to-moderate arterial hypertension. This study was conducted in 40 primary care centres in Spain. 250 patients were included with data for 226. Mean age of participants was 59 years, and around 50% females/males. The no. of diseases was statistically significantly higher in the intervention group 2.6 (s.d=1.6) vs 2.2 (s.d=1.2), p=0.023). Patients in the control group received usual GP care and the intervention group received the intervention from GPs plus an OMRON automatic monitor for HBPM. The programme was measuring their blood pressure 3 days a week (Tuesdays, Thursdays and Saturdays), twice before breakfast and twice before supper and record the results on a card. 74% of the control group and 92% of the intervention group were compliant (measured by MEMS) (95% CI 63.9 to 84.1 and 86.7 to 97.3, p=0.0001); the mean percentage compliances were 87.6% for the control group and 93.5% for the intervention group (95% CI 81.2 to 94.0 and 88.7 to 98.3, p=0.0001); the percentage of days the medicine was taken correctly were 83.6% and 89.4; the percentages of participants taking medicine at the correct time was 79.89 vs. 88.06.

Rudd (2004) [175] (included in the Cochrane updated review) conducted a RCT of a system for patients to monitor their own blood pressure. Patients of two medical clinics in California were randomised to receive routine care (n=76) or

an automated blood pressure device at home with management by a nurse care manager (n=74). The mean age for the intervention was 59 and 60 for the control group. Fifty percent of the intervention and 56% of the control group were female. Patients recorded their blood pressure twice a day at the same time using the semi-automated portable device. At the end of the week the device printed a report of up to 14 measurements and every two weeks patients were to mail the values on the printout to the nurse care manager who used the data to guide medicine therapy. Any new blood pressure medicine initiation was requested from the doctor. The primary outcome was change of BP at 6 months. Secondary analyses were made for frequency of medicine changes and adherence. Adherence was measured by a medicine event monitor (a microchip in the pill bottle lid of the most frequently used medicine) and the patients were required to return to the clinic at 3 and 6 months so this data could be downloaded, although this was not used as feedback to patients, physicians or nurse care managers. The mean daily adherence rate was 80% (s.d=23%) for the intervention group and 69% (s.d=31%) for the control group, p=0.03).

Morice (2001) [243], a study from the Cochrane review, compared an asthma nurse-led intervention with routine care in patients with asthma with negative results. A group of 80 patients (53 women) aged between 16 and 72 years were included in the study. Mean age was 36.1 years. Compared with the control group, patients in the educational intervention group had a minimum of two separate sessions, lasting on average 30 minutes each. These were carried out on an individual basis. The first session involved discussion on the basic mechanisms of asthma, including common triggers and an explanation of the changes which occur to the airways resulting in the symptoms experienced by the patient. This was supported by illustrations in the 'Regular Therapy with Asthma' booklet which was given to each intervention group patient. Lifestyle influences, such as occupation and leisure activities were discussed where appropriate to the individual. The need for 'preventer' and 'reliever' medicine was also emphasised during this session. Patients were encouraged to actively participate in the session and relatives were included at the patients' request. The second session took place on the following day.

Previously given information was briefly summarised with input from the patient as a means of checking understanding. An agreed individualised self-management plan was determined, with written instructions using the 'Sheffield Asthma Card'. This also contained a telephone contact number. Each patient was given a peak low meter to take home and instructions on monitoring, with documentation of predicted peak low measurement and parameters for altering treatment, as well as clear written guidelines on when to seek emergency care. Home intervention was based upon a combination of symptoms, and peak low recordings, and all guidance offered throughout the educational programme was based on the BTS guidelines for the management of asthma in adults [196]. This study was conducted in the UK. There were no statistically significant improvements in compliance at six months.

9 Reviewing medicines

9.1 Recommendations

Hyperlink to Reviewing Medicines

9.2 Introduction

Review of medicines and medicine-taking is seen as an important aspect of health care. Professionals involved in prescribing and dispensing of medicines are currently reimbursed for reviewing medicines. General practitioners in the UK are remunerated for medicine review via the Quality and Outcomes Framework (QOF). Community pharmacists are reimbursed for carrying out reviews which are called Medicines Use Reviews (MURs). The Dispensing Review of Use of Medicines (DRUM) is part of the Dispensing Services Quality Scheme for GP surgeries.

The terminology in this area is not standardised and is subject to change. The Medicines Partnership Programme [8] defined medicine review as 'a structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of medicine-related problems and reducing waste'. It is implicit in this definition that the patient is involved. In 'Room for Review' in 2002 they suggested four levels of medicine review – level 0 which is an ad-hoc opportunistic review; level 1 a prescription review which is a technical review of a patients list of medicines; level 2 is a treatment review which is a review of medicines with the patients full notes and level 3 which is a clinical medicine review which is a face-to face review with patients of medicine and condition. A review with the patient's notes but not necessarily with the patient (as in level 2 as described above) fulfils the criteria for QoF. An MUR is described as a one-one conversation between people and pharmacists that are designed to identify any problems a person is experiencing with their medicines (Pharmacy in England White paper 2008) [2]. Community pharmacists carrying out these reviews will not generally have

---

[8] http://www.npc.co.uk/med_partnership/assets/room_for_review.pdf

access to clinical information about patients. The recent Pharmacy in England White Paper (2008) [2] reports that many people report satisfaction with this service but longer term impacts can not be assessed. The White Paper reports that government plans for MUR services to be prioritised to meet health needs and ensuring funding rewards health outcomes.

The National Prescribing Centre has recently revisited the topic in A Guide to Medicine Review (2008). The guide aims to advise those providing and commissioning medicine reviews. This characterises 3 types of medicine review with an emphasis on the purpose of the review: Type 1 prescription review; Type 2 concordance and compliance review and Type 3 clinical medicine review. The three types of medicine review replace the earlier levels of medicine review. This reclassification appears to make clearer the role of the review and the place of the patient and clinical information in different types of review.

The GDG were interested in whether there was any evidence that medicine review improved either shared decision-making or adherence. In this context medicine review has to involve a face-to-face meeting with professionals and patient. The professional involved was not pre-defined. The evidence search used 'medicine review' as a generic term.

9.3 Does medicine review increase shared decision–making or adherence?

Related references	Evidence statements (summary of evidence)
All retrieved evidence	There is conflicting evidence with regards to whether medicine review increases adherence.
Lowe (2000) [248]; Sturgess (2003) [249]; Bernsten (2001) [250]; Begley (1997) [251]; Nazareth (2001) [252]	Four RCTs conducted in the UK shows that medicine review increased adherence to prescribed medicine. One RCT showed no statistically significant difference in adherence.
Lipton (1994) [253]; Hanlon (1996) [254]; Chisholm (2001) [210]; Taylor (2003) [255]; Grymonpre (2001) [256]; Sookanekun (2004) [257]	There is conflicting evidence from six RCTs conducted outside the UK that medicine review increases adherence to prescribed medicine.
Grymonpre (2001)[256]	Medicine review was carried out by pharmacists in all of the RCTs, except for one RCT where a trained volunteer undertook the review which was then reviewed by a pharmacist consultant.
Lowe (2000)[248]; Hanlon (1996)[254]; Grymonpre (2001)[256]; Nazareth (2001)[252]; Taylor (2003)[255]; Bernsten (2001) [250]; Begley (1997) [251]; Sturgess (2003)	Most of the RCTs included only participants over 65 years old.

9.3.1 Evidence to recommendations

The GDG considered that review of prescribed medicines is most commonly undertaken in clinical settings as part of management of patients and their medical problems. In this setting it is seen as integral to continuing care and not separate from it. The GDG considered that all levels of medicine review as described in 'Room for Review' take place in this setting and have a role. Revisiting a decision to prescribe medicines and exploring patients medicine-taking behaviour was considered by the GDG to be part of the dynamic process that long-term medicine prescribing required.

The research evidence primarily addresses medicine reviews that take place separate from the delivery of clinical care, often by practitioners who do not have access to clinical history and notes. These have been a recent development and have primarily involved pharmacists. Most of the evidence on reviews by pharmacists comes from studies that targeted older adults on multiple medicines. Many studies include quite complex pharmaceutical care programmes where the interventions consists of a number of components including education and follow-up which the GDG considered more intensive than is currently provided in any type of medicine review provided in the UK.

Medicine review can have benefits for the patient but evidence was conflicting whether this led to improvements in adherence to prescribed medicine.

The GDG were particularly concerned that reviews of medicine carried out remote from the clinical settings needed to feed back to clinicians who were involved in prescribing and other aspects of care. Increasing the number of medicine reviews and the personnel involved in carrying them out might not be effective if communication and follow up is not achieved.

The GDG were clear that the lack of research on reviews conducted as part of clinical care should not indicate that these were not of value. Review of medicines will continue to be part of delivery of health care. As responses to medicine can change over time, both in terms of patient behaviour

(adherence) and clinical outcomes, a process of medicine review is likely to be necessary and be part of on-going processes of decision-making and medicine-taking. An informal review of medicine should continue as part of good clinical practice but it is not possible to recommend precise timings for formal medicine reviews outside the clinical setting.

9.3.2 Methods of the evidence review

The titles and abstracts of studies retrieved by an electronic search for medicine review were scanned for relevance to the question of whether medicine review increases adherence to medicines. Any potentially relevant publications were obtained in full text. These were then reviewed to identify the most appropriate evidence to help answer the question and to ensure that the recommendations are based on the best available evidence. This process required four main tasks: selection of relevant studies; assessment of study quality; synthesis of the results; and grading of the evidence.

This paper includes a narrative summary of the included evidence, following the agreed reviewing protocol:

Types of studies - randomised controlled trials (RCTs) of medicine review interventions to increase adherence.

Types of participants - people prescribed medicine for a medical condition. Medicine review performed by any healthcare professional or trained personnel.

Setting - carried out in the community.

Duration of studies - no time limit specified for this evidence review.

Types of interventions - any medicine review (as implying face to face meeting between the patient and the health care professional doing the review) interventions intended to change adherence to prescribed medicine. The content and delivery of interventions are not standardised in the literature. The term 'pharmaceutical care programme' is used and this applies to pharmacist led programmes which assess medicine use, develop an

intervention and provide long term follow-up to patients including liaison with the prescriber. Some of these interventions provide intensive support. Some subjective assessment of studies was required as content is often not well defined. Many of studies on interventions to increase adherence used pharmacists to carry out the intervention but we have included here only studies that were carried out in the community and were providing general review rather than disease specific support.

Types of outcome measures - any prescribed medicine adherence outcomes which changed as a result of the medicine review. Outcomes relevant to patient involvement were reported as part of the evidence review.

9.3.3   Evidence review

Of the RCTs found relating to medicine review, many had to be excluded as they did not have adherence outcomes. Instead they focused on hospital re-admissions, care home admissions, death and cost-effectiveness. One high quality RCT conducted by **Zermansky (2002)** [258] for HTA could not be included as there were no specific adherence outcomes. Zermansky (2002) studied whether a trained pharmacist could conduct effective clinical medicine reviews of elderly patients who were on repeat prescriptions from their GP. The participants were 65 years or over on repeat medicine, who were not resident in a nursing or residential home and were not terminally ill. The study lasted 12 months and the intervention involved the pharmacist assessing the patient, their illnesses and their medicine regimen and making recommendations. The primary outcome measure was the number of repeat medicine changes per patient, which was 2.2 in the intervention group and 1.9 in the control group (Difference of 0.31, 95% CI 0.06 to 0.57), p=0.02). The secondary outcome was the effect on cost of medicine. There was a rise in repeat medicine items for both groups, but this was statistically significantly less for the intervention group (intervention mean 0.2, s.d=1.55; control mean 0.4, s.d=1.53, difference -0.2, 95% CI, -0.4 to-0.1). The cost saving for the intervention group compared to the control group was £4.75 per 28-day month, a total of £61.75 per patient per year.

A systematic review **(Holland 2007)** focusing specifically on pharmacist-led medicine review was found. However the primary outcome of interest was reduction of hospital admissions and deaths in older people and adherence was a secondary outcome. The studies included all forms of medicine review for checking and optimising the patients' medicine regimens apart from those with only knowledge and/or adherence outcomes. They reported that 14 of the trials included adherence, with 7 reporting a statistically significant effect and 7 reporting a statistically non-significant positive effect.

The term 'pharmaceutical care programme' is also used in the literature and this generally applies to pharmacist-led programmes which assess medicine use, develop an intervention and provide long term follow up to patients. Although more intensive that any programmes currently delivered in the UK we included these studies as it was important to assess whether such structured and intensive support was either clinically or cost-effective.

Some subjective assessment of the studies was necessary as the content of the reviews and pharmaceutical programmes is not always clearly defined.

9.3.3.1   RCTs conducted in the UK

Sturgess (2003) [249] measured a structured pharmaceutical care programme provided to elderly patients by community pharmacists 191 elderly patients with a mean age of 73.1 ± 5.0 for the intervention group and 74.2 ± 6.3 for the control group. This RCT was conducted in Northern Ireland. In the intervention pharmacists assessed patients to identify medicine-related problems. A number of information sources were used by intervention pharmacists during this assessment procedure including: the patient (via informal questioning), the patient's GP, study questionnaires and computerised medicine records. During the assessment, pharmacists were asked to document any identified medicine-related problems and to form with the patient an intervention and monitoring plan e.g. education, implementation of adherence improving strategies. Pharmacists visited patients at home to assess storage of medicines where problems were identified.

Self-reported compliance: between-group analysis at each assessment point indicated that a statistically significantly higher proportion of intervention patients were compliant with their medicine at 12 (intervention group: 40.4%, control group: 24.4%) and 18 (intervention group: 47.3%, control group: 14.7%) months compared to control patients (p<0.05) (6 months: intervention group: 34.5%, control group: 29.4%). Analysis of change in compliance during the study (change in compliance status compared to that reported at baseline) showed that a statistically significantly higher proportion of intervention patients changed from non-compliant to compliant compared to control patients (intervention 13.4% vs. control 9.1%) and a statistically significantly higher proportion of control patients changed from compliant to non-compliant compared to intervention patients at 18 months (control 36.4% vs. intervention 4.5%).

Lowe (2000) [248] determined whether a medicine review and education programme influenced elderly patients' compliance and knowledge compared to a control group in a RCT. 161 participants, mean age 77.5 (sd=65-96) for the intervention group and 75 (sd=65-88) for the control group, mainly female (67%), living with spouse or relative 55% (intervention group) and 57% (control group) and prescribed an average of 4 medicines (ranging from 1 to 8). The RCT was conducted in a GP practice in Leeds, UK. An investigator visited patients and filled in a structured questionnaire regarding their medicines, which medicine had been used and patients' understanding and ability to take medicines. The investigator then reported the findings to doctors where there was a need to reduce dosage and discontinue medicine, then liaised with the pharmacist for modifications to medicine containers. At the second visit after a month they delivered 1 months supply of medicine and removed any other prescribed medicines. They discussed the regimen, the purpose of the medicines and the correct way to take them, with the use of a reminder chart if needed. At 3 weeks follow-up participants were given a further months supply and assessed on their knowledge and compliance, by counting the medicines left from the last visit. The mean compliance score was 91.3% for the intervention group (95% CI, 89% to 94%) and 79.5% for

the control group (75% to 84%), which was statistically significantly different (p<0.0001).

N.B This study was under 6 month's duration but the patients were followed up twice at 3 week to monthly intervals and the study was of particular relevance.

Begley (1997) [251] assessed the influence of domiciliary pharmacy visits on medicine management in sample of elderly people recently discharged from hospital to their own homes. Patients were aged 75 years or older. The study included one intervention group receiving home visits and counselling, in which structured patient interviews were conducted during the domiciliary visits and consisted of six sections: patient information; medicine knowledge; Patient dexterity; abbreviated mental test; medicine management; and compliance with medicine regimen. Patients were seen during 12 months. There were two control groups: one which was the control and received visits only (called V group), and other which was the control group that received traditional pharmaceutical services with no visits except for the beginning and the end of the study (NV group).

At each visit there were statistically significant differences between the groups in terms of distribution of patients at the various levels of compliance (p<0.001). Compliance was higher at 3 months and 12 months for the intervention group compared to the other control groups (p<0.001), despite the low compliance value for the intervention group at the 12 month visit. Patients in the intervention group who increased their compliance rates between visits also increased their medicine knowledge scores (p<0.005). Mean scores for medicine knowledge did not differ significantly (statistically) between the groups at any of the visits, although the mean score for the intervention group increased significantly (statistically) between the initial and the two weeks visits (p=0.001). There were no changes for patient dexterity scores between groups at any point of the study. Contacts with GP and health workers was lower for the intervention group than for the control (V) in each of the four time periods (p<0.01).

Bernsten (2001) [250] conducted a multicentre RCT in seven European countries including the UK that evaluated a pharmaceutical care programme provided to elderly patients (aged 65 or older) taking 4 or more medicines by community pharmacists. A total of 1290 intervention patients and 1164 control patients were recruited. The programme interventions included: 1) educating the patient about their medicine regimen and their condition; 2) implementing compliance-improving interventions such as medicine reminder charts; 3) rationalising and simplifying medicine regimens in collaboration with the patients GP. This was a continuous process throughout the 18 months of the study.

Generally, the programme had some positive effects on humanistic health outcomes such as satisfaction with treatment, and sign and symptom control, and on economic outcomes, but had less impact than anticipated on medicine therapy, medicine knowledge and compliance with medicine. An analysis of changes in compliance during the study indicated that at 18 months a statistically significantly higher proportion of the intervention patients changed from being noncompliant to compliant compared with the control groups (p=0.028). Intervention patients rated the services provided higher that the control at 6 and 18 months (p<0.05). There was a small statistically significant increase in satisfaction in the intervention group over time (baseline vs. 12 months p=0.039).

Nazareth (2001) [252] compared patients who had been discharged from hospital with a discharge plan with those who had a standard discharge letter. This RCT included 362 patients from four hospitals in central London. The participants had a mean age was 84 years in both groups (s.d=5.2 and 5.4 respectively), mainly female (62% and 66%), white (97%) with a mean of three chronic medical conditions and prescribed a mean of 6 medicines (s.d=2). The discharge plan included assessing the prescribed medicine, rationalising the medicine and assessing patients' medicine management, knowledge and support. The participants were then followed up 7 to 14 days later at home by community pharmacists who compared medicine-taking with prescribed medicines and their understanding and adherence to the medicine

regimen. They intervened when necessary and provided medicine counselling, disposal of excess medicines and liaison with GPs. There was no statistically significant difference in adherence to medicines for either group at 3 months or at 6 months.

9.3.3.2   RCTs conducted outside the UK

Lipton (1994) [253] assessed the impact of clinical pharmacists' consultations on medicine regimens, compliance, and health service use of 706 geriatric hospitalized patients discharged on 3 or more medicines. The RCT was conducted in the USA. Mean age was 74.6 in the experimental group and 74.4 in the control group. Pharmacists consulted with experimental patients at discharge and 3 months thereafter, and with physicians as needed. Controls received usual care. At 6-8 weeks after enrolment, experimental patients were more knowledgeable about regimens than controls. At 12-14 weeks, they were on fewer medicines and less complex regimens, and had better compliance scores p<0.001). There was no effect on service use or charges, perhaps due to inadequate sample size and lack of targeted medicine group's analysis.

Hanlon (1996) [254] was an RCT which compared the effects on elderly outpatients who had an additional pharmacist intervention with those who received usual care from their physician. Most of the patients were male (98% in the intervention and 100% in the control group), white (79% and 75% respectively), married (65.7% intervention, 85.4% control), with baseline compliance rates of 73% and 74% respectively. The mean age of participants was 70 years old. The RCT was conducted in Durham, North Carolina. Before attending the physician the pharmacist reviewed their medical records and medicine lists to ascertain their current medicine use, medicine-related problems and to evaluate their needs by applying the Medicine Appropriateness Index. Their findings were then reported to the physician. The Pharmacist educated the patient on medicine-related problems and encouraged compliance through strategies such as medicine reminders and written patient materials. They reviewed safe medicine use and the importance of discussing medicines with physicians. There were no

statistically significant differences between the groups at the end of the follow-up period with regard to medicine compliance (77.4% of intervention group and 76.1% of control group complied, p=0.88).

Chisholm (2001) [210] studied the compliance rates of patients who received a clinical pharmacist intervention in addition to usual care compared to control patients after a renal transplant. The RCT included 24 participants, 75% male with a mean of 49 years (s.d=10 years) and 58.3% Caucasian, 37.5% African-American and 1 Hispanic. The RCT was conducted in Augusta, Georgia, USA. The Pharmacist obtained medicine histories and reviewed medicines monthly. They made recommendations to the nephrologists and counselled the patients on their medicine, including instructing how to use the medicine. Patients were encouraged to call them with any questions. The patients were assessed on their understanding of their medicine and advised on how to enhance compliance.

At 12 months the compliance rate was statistically significant for the intervention group 96.1% (s.d=4.7%) compared to the control group 81.6% (s.d=11.5%), p<0.001. For 6 of the 12 months there were differences in compliance rates (64 to 100% for control group and 89 to 100% for the intervention group) with the intervention group always at a higher rate (p<0.05). The duration that patients complied for also differed with the intervention group remaining 75% compliant each month compared to only 33.3% of the control group (p<0.05).

Taylor (2003) [255] conducted an RCT of patients attending a community-based physician and compared those who additionally received a Pharmacist intervention to a control group. The majority of participants were women (63.6% in the intervention group vs 72.2% in the control group, p=0.445), most were white (60.6% vs 61.1%, p=.966) with a mean age of 64.4 and 66.7 years respectively (p=0.467), the majority were married 75.8% vs 72.2 (p=0.935) with 12 years mean education. They were taking on average six medicines each. The RCT was set in medicine clinics in Alabama, USA.

The pharmacists evaluated the patients' medicine, reviewed medical records and examined medicine history to determine compliance and complications with medicine. Therapeutic recommendations were made to the physicians and the pharmacists made follow-up visits to patients, gave individualised education and were available to answer questions. Patients' responses to medicines were monitored and their medicine regimens consolidated, dosage frequency was reduced and medicine reminders and techniques for using certain devices were taught.

The number within the intervention group to have compliance scores of 80-100% increased by 15% but there was no change for the control group (time period not stated). By 12 months this difference was not statistically significant, 100% of patients in the intervention group versus 88.9% (s.d=6.3) of the control group had compliance scores of 80-100%, p=0.115). At baseline this was 84.9% (s.d=6.7) and 88.9% respectively (s.d=5.8, p=0.728).

The most frequently sited reasons for not complying with medicine were forgetting to take the medicines (n=10), having too many to take (n=9), finding it hard to read or understand the directions (n=4) and too much trouble to take (n=4).

Grymonpre (2001) [256] compared the impact on geriatric patients who received pharmaceutical care compared to those patients who did not in a RCT. Most of the patients were female (75% intervention vs 83% control, p=0.254), aged 77 (s.d=8.0 to 9.0), Caucasian (100%) and lived alone 61% vs 77% respectively, p=0.018. The RCT was conducted in a community-based health clinic in Manitoba, Winnipeg, Canada. Volunteers and staff were trained to conduct a comprehensive medicine review which was utilised by the pharmacist to identify and document potential and actual medicine-related issues and to address these with the patient and they physician. Their use of prescribed and non-prescribed medicines, social medicines, home remedies, regimen, adherence and communication with GPs, problems or side effects with medicines were all assessed. The recommendations were given in a letter to physicians and the patients were followed up by the pharmacist when

required to monitor therapeutic endpoints and sort out any problems that had arisen.

The mean number of mediations adhered to at follow-up was 87 ± 46 for the intervention and 85 ± 41 for the control group, p=0.895, showing no statistically significant difference in adherence.

Sookaneknun (2004) [257] compared hypertensive patients assigned to a pharmacist-involved group with those who had no pharmacist involvement, with the objective of stabilising blood pressure. The participants of the RCT included 235 patients, mean age 63 years old and mainly female (64% in intervention and 71% in control group). The RCT was conducted in Thailand. The intervention group's blood pressure was measured every month by the pharmacist and they assessed the patients understanding of medicines, adherence and reviewed adverse effects from the medicines. Medicine counselling was given and medicine-related problems were identified, resolved and prevented. The recommendations for change of medicine regimen were given to the physicians. The adherence at pre-test was not statistically significantly different but at post-test the treatment group had statistically significantly increased adherence compared to the control group, Pre-test adherence of 80% or more was found in 51% of the treatment group and 56% of the control group. At post-test this had increased to 63% for the treatment group and had remained constant (55%) for the control group (p=0.014).

Quality of studies

The quality of many of the RCTs was low. This was mainly due to the possibility of bias occurring within the methodology.

10 Health economics and interventions to increase adherence

10.1 Introduction

Health economics is about improving the health of the population through the efficient use of resources. Economic evaluation provides a formal comparison of benefits and harms as well as the costs of alternative health programmes. It helps to identify, measure, value and compare costs and consequences of alternative treatment options. These outcomes are usually synthesised in cost-effectiveness (CEA) or cost-utility analysis (CUA), which reflect the principle of opportunity costs. For example, if a particular treatment strategy were found to yield little health gain relative to the resources used, then it could be advantageous to re-deploy those resources to other activities that yield greater health gain for the population.

The application of health economics in medicines concordance is more complex and is not as well developed as it is in its more common application to health technology assessment. There is considerable heterogeneity in the course and nature of diseases, in the types of health technologies (medicines, devices etc) used to treat them, and in the nature of possible interventions which may help to improve either decision-making or adherence.

We found that most health economic papers use adherence and compliance interchangeably, despite the conceptual difference in meaning found in the non health economic literature. In a recent economic review paper [259], the authors state that "compliance and adherence imply patient behaviour being congruent with healthcare providers' recommendation". In accordance with this guideline, this chapter will use "shared decision making" (SDM) to describe "a patient centred process where health care professional (HCP) makes a therapeutic alliance with a patient," and adherence for describing "medicine-taking behaviour congruent with prescriber's recommendation". From a health economic perspective the concepts of persistence and forgiveness are potentially more valuable. Persistence is the length of time from initiation to discontinuation of therapy and forgiveness the benefits of a

medicine that persist even when a dose is missed. Health economics perspectives on SDM are discussed in chapter 4.

When considering the costs of interventions to increase adherence from the perspective of the NHS, a health economic evaluation will consider both the direct costs of the intervention itself, and the implications for resource use in terms of use of medicines and health services. The interventions could include, but not necessarily be limited to, one or any combination of the following: devices; packaging; or additional contact time with health care professionals.

The measurement of benefit of adherence enhancing interventions is likely to focus on the measurement of the health benefits derived from any improved adherence to the medicines themselves. The level of benefit will depend on both the effectiveness of the adherence enhancing intervention itself, and on the dose-response related efficacy of the medicine(s) (net of any disbenefits from any adverse events).

In order for an adherence enhancing intervention to be cost-effective from the perspective of the NHS for example, an economic evaluation would need to demonstrate that the intervention impacts on adherence in such a way that brings about a beneficial change in health gain at an acceptable cost or ideally a net cost saving. In accordance with NICE social value judgement criteria, interventions are usually considered to be cost-effective if:

a) The intervention dominates other relevant strategies (that is, it is both less costly in terms of resource use, and more effective compared with the alternative); or
b) The intervention has an incremental cost-effectiveness ratio (ICER) of less than £20,000 per quality-adjusted life-year (QALY) gained, compared with the next best strategy. For interventions with an incremental cost per QALY between £20,000 and £30,000 the probability of the intervention being considered cost-effective will diminish as the ICER rises.

All else being equal, adherence-enhancing interventions for medicines which are less 'forgiving' to nonadherence (**Urquhart, 1996)** [260] (**Girvin, 2004**) [261], for example, will have a higher threshold for them to be considered cost-effective compared to interventions for more 'forgiving' medicines.

The evidence on effectiveness of adherence enhancing interventions is of poor quality overall and provides inadequate evidence on long term follow-up and clinical endpoints. This guideline is a general guideline so given these complexities, and given the time available for development of this Guideline, it was not deemed possible or appropriate to try to develop de novo models designed to estimate the cost-effectiveness of interventions to improve adherence to medicines. Instead, we present an overview of the current literature which we consider to be relevant to the Guideline. In short, the available literature is primarily concerned with reviews of health economic analyses of interventions to improve adherence, whilst other reviews have addressed methodological issues around conducting evaluations concerned with measuring the impact of nonadherence on the cost-effectiveness of medicines.

This chapter is primarily concerned with presenting the methods and the results of literature reviews investigating the cost-effectiveness of adherence enhancing interventions. This is followed by a summary and discussion of the findings including a discussion of some of the methodological issues arising from the reviews. The GDG used the evidence from the reviews when considering the possible cost-effectiveness implications of their recommendations.

10.2 Which Interventions are cost effective in increasing adherence/compliance*?

Related References	Evidence Statements (summary of evidence)
Elliott (2005) [259]; Cleemput (2002) [262]; Hughes (2001) [263]	The evidence from the SRs revealed that a meaningful conclusion from a comparison across studies could not be achieved due to heterogeneity and the general poor quality of included studies. Definitions given for nonadherence were inadequate. Where adherence outcomes were reported, adherence measures varied greatly. A wide range of mostly disease specific health outcomes was used. Methodologies relating to costs were in most studies problematic. Most importantly, it was found that linking improved adherence to improved outcomes has proved problematic.\n\nThe reviews emphasised the importance of standardising the methods to take nonadherence into account when assessing the effectiveness and cost-effectiveness of medicines. Moreover, the necessity to measure adherence and to establish a link to clinical outcome appropriately were highlighted. The need to distinguish persistence from compliance/adherence outcomes was described.

*Please note that, from an economic perspective, adherence and compliance refer to the same concept defined as "the degree to which patient behaviour is congruent with the recommendations of health-care providers"[9], unlike concordance or persistence. For consistency, adherence was used in this review narrative regardless of the terminology choice of the original study.

---

[9] Haynes RB. Determinants of compliance: the disease and the mechanics of treatment. In: Haynes RB, Taylor DW, Sacket DL, editors. Compliance in Health Care. Baltimore, MD: The John Hopkins University Press, 1979:49–62.

10.2.1 Methods of the evidence review

Our primary aim was to conduct a search of the economic literature to investigate the cost-effectiveness of interventions to increase adherence, with a view to informing the key clinical questions to be considered by the GDG for this guideline.

The following literature databases were searched:
- Medline (Ovid) (1966-June 2006)
- Embase (1980-June 2006)
- NHS Economic Evaluations Database (NHS EED)
- PsycINFO
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)

The electronic search strategies were developed in Medline and adapted for use with the other information databases. The clinical search strategy was supplemented with economic search terms. Titles and abstracts retrieved were subjected to an inclusion/exclusion criterion and relevant papers were ordered. No criteria for study design were imposed a priori. Papers initially included were:
- Full/partial economic evaluations.
- Considered patients over 16 years of age.
- Written in the English language.

This process yielded 88 papers, which were obtained in full text and critically appraised by a health economist using a standard validated checklist following the Guidelines Manual 2007 (www.nice.org.uk).

Types of studies: Systematic reviews of cost-effectiveness studies or comparative economic analyses based on modelling or randomised controlled trials (RCTs) of interventions to increase adherence.

Types of participants: people prescribed medicine for a medical condition from healthcare professionals in any health service setting.

Duration of studies: No time limit was applied.

Types of interventions: any interventions intended to change adherence to prescribed medicine.

Types of outcome measures: adherence levels, clinical, cost, and QALY outcomes.

A general descriptive overview of the studies, their quality, and conclusions has been presented and summarised in the form of a narrative review.

10.2.2 Evidence Review

Three systematic reviews were found. Two have been included on the grounds that they include studies which considered interventions designed to improve adherence **(Elliott 2005**[259] and **Cleemput 2002** [262]). A further review **(Hughes, 2001)** [263] investigating the impact of nonadherence on the cost-effectiveness of pharmaceuticals is included in the narrative as it was deemed highly relevant to the guideline. **Elliott (2005)** [259] reviewed 45 economic studies considering the cost-effectiveness evidence base for interventions to increase adherence. The review by **Cleemput (2002)** [262] reviewed eighteen studies with a view to investigating the economics of therapeutic nonadherence, although a number of included studies considered interventions to increase adherence.

Review 1

A UK systematic review by **Elliott (2005)** [259] included 42 studies: 30 from the US; two from the UK; and the remainder from a range of countries. The studies were conducted in 12 different clinical areas (Table 1). The reviewers used a variety of minimum quality criteria comprising economic evaluation quality criteria, standard hierarchies of evidence, and adherence-specific design issues. 21 of the original studies were based on RCTs, of which 4 used modelling techniques.

Definition of intervention

The interventions described in the reviewed studies employed a large variety of designs. They included programmes to improve convenience of care,

information, counselling, reminders, self-monitoring, reinforcement, family therapy, and other forms of additional supervision or attention. Some design issues arose, such as confounding factors on effect measures where interventions had effects that were not exclusively due to changes in medicines adherence.

Table 1. Studies included in the Elliott (2005) [259] systematic review, with number of studies by intervention and disease. Adapted with permissions from paper: Elliott (2005). Cost-effectiveness of adherence-enhancing interventions: a quality assessment of the evidence. *The annals of pharmacotherapy*, 39(3), 508-515.

Types of intervention	Asthma	Psychotic illness or depression	Hypertension	Diabetes	Tuberculosis	COAD	Malaria	HIV	Other morbidities
Health education or training	12	8	5	2		1	1		4
Specific use of health care professionals	4	4	1	2					4
Telephone calls		3	1						2
Directly Observed therapies					4				
Carers Involved		1	2						
Adverse Drug events		2							
Videos		1							
Work based care			1						
Palatable formulation							1		
Free drugs				1					
Reminders other than telephone or DOT								1	

Definition of adherence and clinical outcome

Apart from the variable and sometimes problematic definition of the intervention to increase adherence itself, the delivery of the intervention differed considerably between studies. Most interventions to increase adherence contained input by a specified health professional, an educational component, and often used of more than one component. The authors found that previously validated and unvalidated adherence measures were used combined with a range of outcome measures.

Study findings

The review does not report the cost-effectiveness findings of the individual studies, but instead concentrated on critiquing the variability and prevailing inadequacy of the methods used.

A number of health economic methodological problems, found in many of the included studies have been highlighted including:

- inappropriate or lack of incremental analysis;
- missing or inadequate sensitivity analysis and quantification of uncertainty;
- missing or unclear stating of the perspective of evaluation;
- appropriateness of statistical analysis for cost data and costing methodologies;
- missing or unclear discounting methods.

For example, of the 42 studies reviewed by Elliott (2005) [259], only nine conducted a sensitivity analysis to quantify the degree uncertainty around the base case results. Moreover, no study assessed how the use of a particular adherence measure or level influenced the base case results. The omission of sensitivity analyses is an important methodological omission which limits the generalisability of the original analyses.

Discussion

Overall, the review found that a meaningful comparison across studies was not possible due to heterogeneity and methodological weaknesses in many studies. A wide range of mainly disease specific outcomes was used. Six

studies did not report outcomes at all. Moreover, there appears to be little consensus across studies about which adherence measures to use. Twenty-four studies did not report results for adherence, or made assumptions about how adherence was improved by the intervention. Most crucially, the review found that linking improved adherence to improved outcomes has proved problematic.

Review 2

A systematic review by **Cleemput (2002)** [262] included 18 studies on the economics of therapeutic nonadherence, which were assessed according to their definition and measurement of medicines nonadherence, study design, and identification and valuation of costs and outcomes. The majority of articles dealt exclusively with medicines nonadherence. Eight studies examined the economics of adherence enhancing interventions. Of these, three were excluded from this review on methodological grounds.

Studies: methods and methodological problems

The reviewed papers included different types of economic evaluations, including cost-effectiveness, cost-benefit, and more descriptive cost-consequence analyses. Time horizons were less than 18 months in all studies, such that long-term benefits of adherence-enhancing interventions can rarely be shown. Costing methods were often found to be inappropriate. Methodological problems related to the definition and measurement of medicines nonadherence, study design, outcome measurement, and consideration of determinants of nonadherence and adherence-enhancing interventions were reported.

Definition of interventions

As set out in table 2, most interventions that represented interventions to increase adherence consisted of single components or combinations of counselling, patient education, reminders, less complex treatment regimens, and other forms of increased supervision.

Table 2: Studies from Cleemput (2002) [262] review, indicating disease group and type of intervention. Details of each study can be seen in table 3. Adapted with permissions from: Cleemput (2002). A review of the literature on the economics of noncompliance. Room for methodological improvement. *Health Policy*, 59(1), 65-94.

Disease Group	Health Education or training	CBT, cognitive approaches	Telephone calls	Directly Observed Therapy	Involve Carers	Palatable formulation	Support Group
Asthma	>		>				>
Psychotic Illness		I					
Hypertension	$	$			$		
Tuberculosis				*			
Malaria						^	

Definition of adherence and clinical outcome

Medicines nonadherence was found to be often ill-defined and not measured accurately. Interruption or cessation of therapy was often used as a definition of nonadherence, but concepts like 'taking less medicines than prescribed' and 'not starting therapy' were also found. Often, nonadherence is not specified at all. None of these five studies appear to have linked adherence to clinically relevant outcomes or QALYs.

Result from studies

No single approach has a clear advantage compared with another. Some of the reviewed studies on interventions to increase adherence show an improvement in terms of cost savings or improved adherence. The review found that one study on an intervention to increase adherence for antimalarials and one for antihypertensives showed some increase in the efficiency of treatment. However, the cost-effectiveness of an intervention to increase adherence will depend upon the costs and health effects associated with usual care and the intervention's own costs and health effects, and so the net effect on cost-effectiveness is unclear. The measures used and results found are presented in Table 3.

Table 3: Details from some of included studies representing interventions to increase adherence, taken from Cleemput (2002) [262]. Adapted with permissions from Cleemput (2002) A review of the literature on the economics of noncompliance. Room for methodological improvement. *Health Policy*, 59(1), 65-94.

ID	Subject	Design	Nonadherence Measure	Effectiveness Measure	Incremental Cost Effectiveness Ratio Results
>	Medication and inhaler compliance intervention for patients with asthma	Cost Effectiveness	Self Report	Improvement in adherence score	No ICER presented. Intervention appeared to be cost effectiveness.
I	Medication and inhaler compliance intervention for patients with psychosis	Cost Outcome Description	Self Report	Compliance, insight, attitude towards medication, global functioning	No ICER presented. No reported differences in costs – some correlations reported.
$	Medication and inhaler compliance intervention for patients with hypertension	Cost Benefit	Self Report	Prevented indirect earnings, prevented direct medical costs.	No ICER presented. Cost benefit ratios were 2.2 for family member re-enforcement and 1.24 for family member re-enforcement plus message clarification for the patient. The later was more favourable.
^	Malaria chemoprophylaxixis	Cost Effectiveness	Urine Specimen	Adherence achieved	No ICER presented. Cost Effectiveness ranged from $1.2 to $1.67

Discussion

The review described the important nonlinearity in the relationship between quality of life and nonadherence. Nonadherence may improve patients' quality of life, for instance when they deliberately adapt their medicine schedule to their own lifestyle, or it may decrease their quality of life due to increased morbidity, adverse events and/or side-effects. From a pharmacological perspective, under-dosing or extended time intervals between two medicine intakes may increase morbidity (and subsequently costs), whereas over-

dosing or shorter intervals between two medicine intakes may increase unpleasant side-effects or toxicity of the medicine.

The authors highlight the importance for clinicians, policymakers, and patients to consider the impact of nonadherence on the cost-effectiveness. Methodologies to do this adequately need to be improved and used in a standardised way in future work.

Review 3

A systematic review of pharmacoeconomic evaluations conducted in the UK by **Hughes (2001)** [263] included only studies that applied sensitivity analyses to adherence rates in order to evaluate the impact of nonadherence on the cost-effectiveness of different medicines. 22 evaluations were included in the review, of which 13 were from the US, 5 from Canada, and 2 were UK studies.

Studies: methods and methodological problems
Included studies were concerned mainly with treatments for chronic diseases, although two considered medicine regimen nonadherence with acute diseases. Decision analytic models were employed in most cases, and some of the evaluations modelling chronic illnesses adopted a Markov model approach. It was not specified if models were based on one trial exclusively or on multiple sources. Time horizons varied considerably between studies and ranged from 2 weeks to lifetime, with 3 studies spanning time up to 1 year, and 10 papers of over 10 years. Effectiveness measures varied, including disease specific outcomes such as 'fractures avoided' to more generic QALYs. The vast majority of studies conducted insufficient sensitivity analysis, particularly of adherence rates.

Definition of nonadherence and clinical outcome
The review indicated that definitions used for nonadherence were inadequate. Six studies made no attempt at defining the measure of adherence, or used an arbitrary proportion of doses taken to define whether patients were to be considered non-compliant. Similar to the other two reviews, inadequacy exists

in terms of sources of adherence rates used in the evaluations. Over a third of the included studies used values based on assumptions, or on medical opinion, or did not state the sources of the adherence data.

Linking nonadherence to clinical outcomes was problematic. Many studies were found to link nonadherence to changes in risk probabilities or outcomes, but only four referenced an evidence based source. Of those studies which presented sources for values and assumptions, very few used sources other than opinion. Few provided any indication of the differences in health benefits which likely to be observed when patients were non-compliant.

Discussion

It was not possible for the review to compare the magnitude of the impact of nonadherence among different medicine-disease combinations. However, it was found that the nature of nonadherence, the severity, and pathophysiology of the disease, and the extent to which a medicine 'forgives' nonadherence, (the ability of a drug to sustain its pharmacological action after a dose has been missed), all contribute to determining the extent of the clinical and economic consequences of nonadherence.

In terms of the review findings, studies showed that nonadherence generally results in a reduction in efficacy. The relationship between nonadherence and cost was less clear. While eight of the reviewed studies show that costs increase as adherence decreases, six found the opposite trend. This difference did not appear to be related to the nature of the disease, the measure of nonadherence, or the assumptions relating to the health benefits experienced by non-compliers.

The authors emphasise the need to systematically include nonadherence in pharmacoeconomic evaluations. The vast majority of studies were based upon trials designed to demonstrate efficacy, and not effectiveness. While the randomised clinical trial remains the 'gold standard' for comparing alternative treatments, the high internal validity required to demonstrate efficacy comes

at the expense of external validity, that is, generalisability of results to the 'real world' of medical practice.

10.3 Update of the systematic review by Elliott (2005)[259]

10.3.1 Methods of the evidence review

The aim of this literature search is to update the systematic review by **Elliott (2005)** [259] with relevant papers published from 2004 onwards. The titles and abstracts of records retrieved by the searches, suggested by the GDG, or submitted by stakeholders were scanned for relevance to the key questions. Any potentially relevant publications were obtained in full text. This yielded eight papers, which were then reviewed to identify the most appropriate evidence to inform consideration of the key clinical questions. This process required three main tasks: selection of relevant studies; assessment of study quality; synthesis of the results. Three of the eight references were subsequently excluded as they either failed to describe and impute adherence as an outcome measure, or did not meet the methodological requirements. The resulting five papers were reviewed using systematic, transparent approaches following the Guidelines Manual 2007 (www.nice.org.uk).

Types of studies: Systematic reviews of cost-effectiveness studies or comparative economic analyses based on modelling or randomised controlled trials (RCTs) of interventions to increase adherence.

Types of participants: people aged 16 and over prescribed medicine for a medical condition from healthcare professionals in any health service setting.

Duration of studies: No time limit was applied.

Types of interventions: any interventions intended to change adherence to prescribed medicine.

Types of outcome measures: adherence levels as well as clinical, cost and QALY outcomes.

10.3.2 Update evidence review

Five papers were found and included. One paper by **Bosmans (2007)** [264] assessed the cost-effectiveness of a pharmacy based coaching programme to improve adherence to antidepressants. Another paper by **Cleemput (2004)** [265] compared renal transplantation with haemodialysis for patients with renal failure. A paper by **Brunenberg (2007)** [266] examined the cost-effectiveness of an adherence-improving programme comprising monitoring system and adherence training for patients on antihypertensives. One US paper by **Edwards (2005)** [267] assessed the cost-effectiveness of long acting risperidone compared to other oral agents in patients with schizophrenia in a decision model. Finally **Munakata (2006)** [268] evaluated a hypothetical ceiling cost for an adherence enhancing intervention to be cost-effective for HIV positive patients on HAART.

The first Dutch based cost-effectiveness analysis by **Bosmans (2007)** [264] was based on a RCT of 151 patients with a prescription for non-tricyclic antidepressants from their GP for depressive complaints. They were randomised to receive either an intervention consisting of three personal coaching contacts with a pharmacist and an educational video to take home, or alternatively, to usual care including standard oral and written information. Adherence was measured using an electronic pill container (eDEM) and was the primary outcome, with the Hopkins depression 13 item subscale (SCL) used as a secondary outcome measure.

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% to +9.8%). In respect to the SCL subscale, there was no statistically significant difference between the groups despite a slight improvement in the pharmacist intervention group (-0.15, 95% CI -0.54 to 0.23).

The ICER for coaching and education by the pharmacists compared with usual care was €149 per 1% improvement in adherence, and €2,550 per point improvement in the SCL depression mean item score. Uncertainty was

considerable, reflected by insignificance of mean differences. Pairs of costs and effects were distributed in all four quadrants of the cost-effectiveness plane and the cost-effectiveness acceptability curve (CEAC) for adherence showed great uncertainty. As such, the cost-effectiveness of coaching and education by pharmacists as a means of increasing adherence to antidepressants compared with usual care is unclear.

A cost-utility analysis by **Cleemput (2004)** [265] compared interventions for renal failure using a decision analytic model. The model drew on data from a prospective study of 126 adults with chronic renal failure and varying adherence levels. Of these, 23 received renal transplant. Adherence to immunosuppressants for the transplant patients was measured using an electronic event monitoring (EEM) device. Five (22%) study subjects were defined as nonadherent.

Lifetime costs after transplantation in the adherent patient group are higher than lifetime costs in the non adherent group, mainly because adherent patients live longer after transplantation. Compared with dialysis, renal transplantation offers better outcome in both adherent and nonadherent patients. Transplant was shown to be more cost-effective (dominant) than haemodialysis for all adherence levels considered. When full adherence is assumed, transplant generates a cost saving relative to dialysis and gives 5.19 additional QALYs. In a heterogeneous group of adherent and nonadherent patients, the saving was greater, but fewer additional QALYs were generated (5.06). This was mainly due to a reduced survival. Among transplant patients, adherence with immunosuppressants after transplantation is associated with a QALY gain, albeit at a higher cost which was mainly due to longer survival. Mean incremental costs per QALY in adherent patients relative to nonadherent patients after transplantation amounted to €35,021 (95%CI €26,959 to €46,620). Acknowledging that this modelling study may not be generalisable to the UK health care setting, using a threshold willingness to pay of £20,000 per QALY, this study implies that interventions to improve adherence for renal transplant patients may not be considered cost-effective using current UK thresholds.

A cost-utility study by **Brunenberg (2007)** [266] evaluated a medication events monitoring system (MEMS) plus adherence training compared with usual care alone for patients on antihypertensives. Follow-up was for 5-months only. The MEMS is a medicine container and cap equipped with a microchip that registers the date and time of each opening. This study was based on a randomised controlled trial supplemented by non-parametric bootstrapping methods. There were 164 hypertensive patients in the MEMS arm, and 89 in usual care group and they had a systolic blood pressure (BP) >160mm Hg and/or diastolic BP >95mm Hg despite being drug eligible. Unsatisfactory adherence was defined as less than 85% of days taking the prescribed dose. From the healthcare perspective, electronic monitoring led to a reported cost saving of €100 per patient, and an additional 3.1% of patients achieved normal blood pressure than in the usual care arm. The intervention was therefore dominant over usual care. However, sensitivity analysis revealed considerable uncertainty although 55% of point estimates were in the intervention dominating south-east quadrant of the cost-effectiveness plane. The base case societal cost per QALY estimate was €15,667, which is likely to be within the current UK threshold of cost-effectiveness. 33% of bootstrap point estimates were in the south-east quadrant of the cost-effectiveness plane, although 11% were in the dominated north-west quadrant. Overall, effect sizes were small and not statistically significant. The adherence enhancing intervention was considered to be moderately cost-effective but with considerable uncertainty around the base case result. Moreover, given the chronic nature of hypertension, the length of follow-up of five months appears insufficiently short to predict the long-term effect of the intervention on adherence and other outcomes.

Edwards (2005) [267] conducted a cost-effective analysis based on a decision analytic model that compared long acting risperidone with a range of other antipsychotic agents, including oral risperidone and depot haloperidol. The population was drawn from patients with schizophrenia in community dwellings who have previously suffered relapse requiring hospitalisation. Adherence was assumed to be improved by the long acting injectable risperidone formula. It was estimated that a 20% point difference in adherence

would predict a 3.1 point improvement in the PANSS (Positive and Negative Syndrome Scale for Schizophrenia). Such improvement in turn stabilised patients so that a further 6.1 point in PANSS was achieved by further improved medicine-taking behaviour, and aversion of relapse. The model predicts that patients receiving long acting risperidone will have the best clinical outcomes in terms of the frequency and duration of relapses over the one year duration. For example, on long acting risperidone, 26% of patients were modelled to experience relapse requiring hospitalisation, and 24% relapse not requiring hospitalisation. On haloperidol nearly two-thirds of patients are predicted to have relapses requiring hospitalisation, and over 60% relapse not requiring hospitalisation. In terms of days of relapse averted, this analysis predicts dominance of long acting risperidone over the comparators, (that is, better outcomes and lower costs), over the one year time horizon. Univariate sensitivity analysis was reported to have been robust. However, at the upper bound of the 95% CI for relapse rates requiring hospitalisation, there was an ICER of US$821 per day of hospitalisation averted for long acting risperidone compared to oral risperidone. The model also appears sensitive to the cost of hospitalisation and rates of relapse. In summary, the analysis seems of interest, however, there are issues with its robustness and its generalisability to the UK. The outcome of cost per day of hospitalisation averted, poses a challenge for the interpretation of the findings in the context of this guideline. Values used in the sensitivity analysis seem relatively conservative. The short time horizon could be an issue, but has not been thoroughly discussed. Quantifying treatment and quality of life losses in a single measurement such as the QALY may have helped in considering the generalisability of this evaluation to the UK.

A cost-utility analysis conducted by **Munakata (2006)** [268] was based on a decision analytic model. The aim of the study was to quantify the clinical and economic effects of nonadherence, and estimate the cost-effectiveness of improving adherence in treatment naïve patients. For this, HAART treatment with an assumed good adherence was compared with HAART on 'typical' adherence. The authors drew on data from randomised controlled trials and observational data for the comparators, respectively. The model population

was HIV positive, with a mean age of 33. The assumed portion of medicines consumed of 0.98 (0.95-1.0) was defined as adherent, and 0.55 (0-0.95) as nonadherent. The proportion of adherent patients in the typical comparator arm was imputed as 0.52 (0.3-0.88). Lifetime discounted costs in the typical and ideal scenarios were $308,000 and $341,000, respectively. This gives an incremental cost of $33,000. People in the ideal scenario generated 10.2 QALYs per patient compared to 9.0 QALYs per patient in the typical scenario. This gives an incremental effect of 1.2 QALYs. The incremental cost effectiveness ratio (ICER) resulted in $29 400 per QALY. This result indicates that from a cost-effectiveness perspective, there is scope for an intervention to increase adherence. The authors calculated a willingness to pay (WTP) ceiling value for an intervention to increase adherence. They conclude that $1,600 could be spent per patient to increase adherence to ideal levels, giving 15-33% reductions in treatment failure. Univariate sensitivity analysis was conducted for all parameters, as well as multivariate SA for selected values. The analysis was described as robust in sensitivity analysis. In severe diseases where adherence and related comorbidities are influential, adherence improving interventions may be cost-effective. Given that there are interventions that are effective in increasing adherence, this analysis found that $1,600 per patient could be spent on the modelled patient group.

10.4   Summary and Discussion

The initial review included three systematic reviews of literature investigating the health economics of adherence. Only one of these Elliott (2005) [259] was specifically focused on investigating interventions to improve adherence, although the SR by Cleemput (2002) [262] also included interventions to increase adherence. A third SR by Hughes (2001) [263] focused on the investigating the influence of nonadherence on cost-effectiveness of pharmaceuticals.

The interventions described in the reviewed studies covered a range of disease areas and included a variety of designs and methods of delivery. Both validated and unvalidated measures of adherence were employed, and in

some cases the definition of nonadherence was not reported or was arbitrary. The included studies employed a range of mainly disease specific outcome measures. Some studies did not report clinical outcomes at all. There was a lack of good quality evidence linking improved adherence to improved health outcomes, with many of the studies relying on assumptions. Many of the studies had short time horizons, which could be problematic for chronic conditions where long-term adherence is of interest. None of the evaluations considered process utility. Methodological weaknesses from a health economic evaluation perspective included: inadequate use of sensitivity analysis; omission of incremental analysis; and appropriate costing methods.

The SRs indicated that because of the disparity in the nature of the outcomes, the measures of nonadherence used and time horizons of the studies evaluated, it was not possible to compare the magnitude of the impact of nonadherence among different medicine-disease combinations. However, it was evident that nonadherence impacts adversely on efficacy, but its impact on costs varies substantially. Where nonadherence impacts adversely on survival, quality of life, and, or resource usage, there is scope for an intervention that effectively raises adherence. The systematic reviews presented in this Guideline emphasised the importance of standardising the methods to take nonadherence into account when assessing the effectiveness and cost-effectiveness of medicines.

A search for economic evaluations of interventions to increase adherence undertaken for this guideline, and designed to update the search conducted by Elliott (2005) [259], found five recent economic evaluations of interventions to increase adherence. The cost-effectiveness of a pharmacist coaching intervention for patients suffering from depression is unclear, in that the outcome measure used was depression specific, and there was considerable uncertainty in the calculated ICER. The model-based analysis concerned with adherence to immunosuppressants for renal transplant patients appears likely not to be considered cost-effective, but again the direct relevance in the UK context is not certain. The adherence training intervention for antihypertension patients appears to be "moderately cost-effective" although the follow-up may

be too short and again the analysis contained considerable uncertainty and was not UK specific. The dominant result for long acting risperidone in schizophrenia patients using a US-based modelling analysis, is likely to imply cost-effectiveness in a UK context, although the limited sensitivity analysis indicated sensitivity to hospitalisation costs and assumed relapse rates. The modelled analysis for HIV patients on HAART indicates that there is likely to be scope for an adherence enhancing intervention to be cost-effective for this patient group. The absolute ceiling and the uncertainty around the base case value in the UK context is again unclear.

The picture emerging from the economic evaluations found in the update search is unclear, particularly for UK decision makers. None of the evaluations were UK-based, and some included disease specific outcome measures rather than the NICE preferred QALY outcome. A priori, we might expect that interventions to increase adherence for medicines for which nonadherence might have short term survival or more serious quality of life implications, would have a better chance of demonstrating cost-effectiveness, compared to more 'forgiving' medicines. The results of the studies examining adherence interventions for HAART (Munkata 2006) [268] and for risperidone (Edwards 2005) [267] support this supposition. On the other hand, it might therefore be surprising that the study of the use of immunosuppressants (Cleemput (2004) [265] implied that an intervention to increase adherence might not be cost-effective for renal transplant patients. An intervention to increase adherence for the relatively 'forgiving' antihypertensives was indicated to be 'moderately cost-effective.

In short, there appears to be little good quality evidence evaluating the cost-effectiveness of adherence enhancing interventions, or evaluating the impact of nonadherence on cost-effectiveness of medicines. The published systematic reviews have been critical of the quality of the existing economic evidence base, and have tended to focus on critiquing methods rather than reporting cost-effectiveness per se. In particular, there appears to be little information to support UK decision makers. Few of the published economic evaluations were conducted from the perspective of the UK NHS. Methodological weaknesses including inadequate or missing sensitivity analyses, and also the predominance of disease specific outcome measures

instead of QALYs, makes it difficult to generalise the findings of many of the studies to the UK context.

In general, and in particular for the UK context, there is a clear need for more and better research into the implications of nonadherence on the cost-effectiveness of medical interventions, and also to assess the potential of interventions to increase adherence to improve healthcare outcomes and/ or reduce healthcare costs. Future research in this area should ensure that standard principles of good economic evaluation are employed. Models might be used to investigate general or specific adherence cost-effectiveness issues, particularly for chronic conditions where medicine-taking is long-term, and where economic evaluations may need to extrapolate from shorter term clinical trial results. Any such models must ensure that parameter uncertainty is addressed adequately using appropriate sensitivity analysis. Improving the evidence base regarding the inter-relationships between adherence and health and economic outcomes, and using this information appropriately in health economic models will improve the quality of the evaluations, provide better quality information to decision makers, and hopefully lead to improved allocation of limited NHS resources.

11   Bibliography

(1)   Horne R, Weinman J, Barber N, Elliott R, Morgan M. Concordance, adherence and compliance in medicine-taking. Report for the National Co-ordinating Centre for NHS Service Delivery and Organisation R & D. 2005.

(2)   Department of Health. Pharmacy in England, building on strengths - delivering the future. 1-141. 2008.

(3)   Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. Cochrane Database Syst Rev 2008;(CD000011).

(4)   Horne R. Compliance, adherence, and concordance: implications for asthma treatment. Chest 2006; 130(1 Suppl):65S-72S.

(5)   Horne R. Compliance, adherence and concordance. In: Taylor KHG, editor. Pharmacy Practice. Taylor and Francis; 2001. 165-184.

(6)   World Health Organization. Adherence to long-term therapies; evidence for action. 2003. WHO.

(7)   Pound P, Britten N, Morgan M, Yardley L, Pope C, Daker-White G et al. Resisting medicines: a synthesis of qualitative studies of medicine taking. Soc Sci Med 2005; 61(1):133-155.

(8)   Bain D. Doctor-patient communication in general practice consultations. Med Educ 1976; 10:125-131.

(9)   Tuckett D, Boutlon M, Olson C, Williams A. Meetings between experts: an approach to sharing ideas in medical consultation. Tavistock Publishers; 1985.

(10)   Charles C, Gafni A, Whelan T. Decision-making in the physician-patient encounter: revisiting the shared treatment decision-making model. Soc Sci Med 1999; 49(5):651-661.

(11)   Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango). Soc Sci Med 1997; 44(5):681-692.

(12)   Mead N, Bower P. Patient-centredness: a conceptual framework and review of the emprirical literature. Soc Sci Med 2000; 51(7):1087-1110.

(13)   Elwyn G, Edwards A, Mowle S, Wensing M, Wilkinson C, Kinnersley P et al. Measuring the involvement of patients in shared decision-making: a systematic review of instruments. [Review] [88 refs]. Patient Educ Couns 2001; 43(1):5-22.

(14)   Duggan PS, Geller G, Cooper LA, Beach MC. The moral nature of patient-centeredness: is it "just the right thing to do"?. [Review] [36 refs]. Patient Educ Couns 2006; 62(2):271-276.

(15)   Gravel K, Legare F, Graham ID. Barriers and facilitators to implementing shared decision-making in clinical practice: a systematic review of health care professionals perceptions. Implement Sci 2006; 1(16):1-12.

(16)   Thompson AG. The meaning of patient involvement and participation in health care consultations: a taxonomy. Soc Sci Med 2007; 64(6):1297-1310.

(17)   Richards C, Coulter A. Is the NHS becoming more patient centred: trends from the national surveys of NHS patients in England 2002-07. 2007. Picker Institute.

(18)   Murray E, Charles C, Gafni A. Shared decision-making in primary care: tailoring the Charles et al. model to fit the context of general practice. [Review] [32 refs]. Patient Educ Couns 2006; 62(2):205-211.

(19)   Horne R, Weinman J. Concordance, A Partnership in Medicine Taking. The Pharmaceutical Press; 2004.

(20)   Stevenson FA. General practitioners' views on shared decision-making: a qualitative analysis. Patient Educ Couns 2003; 50(3):291-293.

(21)   Haynes TB, Taylor DW, Sackett DL. Behavioural Strategies for improving compliance. In: Haynes TB, Taylor DW, Sackett DL. Compliance in Health Care. John Hopkins University Press; 1979. 174-190.

(22)   Towle A. Physician and patient communication skills: competencies for informed shared decision-making. Vancouver, Canada: University of British Columbia; 1997.

(23)   Elwyn G, Edwards A, Dwyn R, Grol R. Towards a feasible model for shared decision-making: focus group study with general practice registrars. Br Med J 1999; 319:753-756.

(24)   Edwards A, Elwyn G. Inside the black box of shared decision making: distinguishing between the process of involvement and who makes the decision. Health Expect 2006; 9(4):307-320.

(25)   Cox K, Britten N, Hooper R, White P. Patients' involvement in decisions about medicines: GPs' perceptions of their preferences. Br J Gen Pract 2007; 57(543):777-784.

(26)   Légare F, Ratte S, Stacey D, Kryworuchko J, Gravel K, Turcot L et al. Interventions for improving the adoption of shared decision making by healthcare professionals. Cochrane Database Syst Rev 2008;(3).

(27)   Makoul G, Clayman ML. An integrative model of shared decision making in medical encounters. Patient Educ Couns 2006; 60(3):301-312.

(28)   Cox F, Stevenson N, Brtten N, Dundar Y. A systematic review of communication between patients and health care professionals about medicine-taking and prescribing. Medicines Partnership . 2004. Medicines partnership.

(29)   Rao JK. Communication interventions make a difference in conversations between physicians and patients: a systematic review of the evidence. Med Care 2007; 45(4):340-349.

(30)   Lewin SA, Skea ZC, Entwistle V, Zwarenstein M, Dick J. Interventions for providers to promote a patient-centred approach in clinical consultations. Cochrane Database Syst Rev 2001;(CD003267).

(31)   Harrington J, Noble L. Improving patients' communication with doctors: a systematic review of intervention studies. Patient Educ Couns 2004; 52(1):7-16.

(32)   Kinnersley P, Edwards A, Hood K, Cadbury N, Ryan R, Prout H et al. Interventions before consultations for helping patients address their information needs. Cochrane Database Syst Rev 2007;(CD004565).

(33)   Loh A, Simon D, Wills CE, Kriston L, Niebling W, Härter M. The effects of a shared decision-making intervention in primary care of depression: a cluster-randomized controlled trial. Patient Educ Couns 2007; 67(3):324-332.

(34)   Wetzels R, Harmsen M, van WC, Grol R, Wensing M. Interventions for improving older patients' involvement in primary care episodes. Cochrane Database Syst Rev 2007;(CD004273).

(35)   Wetzels R, Wensing M, van WC, Grol R. A consultation leaflet to improve an older patient's involvement in general practice care: a randomized trial. Health Expect 2005; 8(4):286-294.

(36)   Little P, Dorward M, Warner G, Moore M, Stephens K, Senior J et al. Randomised controlled trial of effect of leaflets to empower patients in consultations in primary care. Br Med J 2004; 328(7437):441-444.

(37)   Wilkinson CR, Williams M. Strengthening patient-provider relationships. Lippincotts Case Manag 2002; 7(3):86-99.

(38)   Ross SE, Moore LA, Earnest MA, Wittevrongel L, Lin CT. Providing a web-based online medical record with electronic communication capabilities to patients with congestive heart failure: randomized trial. J Med Internet Res 2004; 6(2):e12.

(39)   Ende J, Kazis L, Ash A, Moskowitz MA. Measuring patients' desire for autonomy: decision making and information-seeking preferences among medical patients. J Gen Intern Med 1989; 4(1):23-30.

(40)   Langewitz W, Nübling M, Weber H. Hospital patients' preferences for involvement in decision-making: a questionnaire survey of 1040 patients from a Swiss university hospital. Swiss Med Wkly 2006; 136(3-4):59-64.

(41)   Tortolero LG, Byrd T, Groff J. Relationship between english language use and preferences for involvement in medical care among Hispanic women. J Womens Health 2006; 15(6):774-785.

(42)   Neame R, Hammond A, Deighton C. Need for information and for involvement in decision making among patients with rheumatoid arthritis: a questionnaire survey. Arthritis Rheum 2005; 53:249-255.

(43)   Braman AC. Patient personality predicts preference for relationships with doctors. Personality and Individual Differences 2004; 37(4):815-826.

(44)   Doherty C, Doherty W. Patients' preferences for involvement in clinical decision-making within secondary care and the factors that influence their preferences. J Nurs Manag 2005; 13(2):119-127.

(45)   Schneider A, Wensing M, Quinzler R, Bieber C, Szecsenyi J. Higher preference for participation in treatment decisions is associated with lower medication adherence in asthma patients. Patient Educ Couns 2007; 67(1-2):57-62.

(46)   Hill SA, Laugharne R. Decision making and information seeking preferences among psychiatric patients. J Ment Health 2006; 15(1):75-84.

(47)   Caress A. Patient roles in decision-making. Nurs Times 1997; 93(31):45-48.

(48)   Degner L, Sloan J. Decision making during serious illness: what role do patients really want to play? J Clin Epidemiol 1992; 45:941-950.

(49)   Hamilton W, Russell D, Stabb C, Seamark D, Campion-Smith C, Britten N. The effect of patient self-completion agenda forms on prescribing and adherence in general practice: a randomized controlled trial. Fam Pract 2007; 24(1):77-83.

(50)   Horne R. Beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of mediciation. Psychol Health 1999; 37(2):113-124.

(51)   Menckeberg TT, Bouvy ML, Bracke M, Kaptein AA, Leufkens HG, Raaijmakers J-AM et al. Beliefs about medicines predict refill adherence to inhaled corticosteroids. J Psychosom Res 2008; 64(1):47-54.

(52)   Horne R, Cooper V, Gellaitry G, Date HL, Fisher M. Patients' perceptions of highly active antiretroviral therapy in relation to treatment uptake and adherence: the utility of the necessity-concerns framework. J Acquir Immune Defic Syndr 2007; 45(3):334-341.

(53)   Brown C, Battista DR, Bruehlman R, Sereika SS, Thase ME, Dunbar JJ. Beliefs about antidepressant medications in primary care patients: relationship to self-reported adherence. Med Care 2005; 43(12):1203-1207.

(54)   Khanderia U, Townsend KA, Erickson SR, Vlasnik J, Prager RL, Eagle KA. Medication adherence following coronary artery bypass graft surgery: assessment of beliefs and attitudes. Ann Pharmacother 2008; 42(2):192-199.

(55)   Kumar K, Gordon C, Toescu V, Buckley CD, Horne R, Nightingale PG et al. Beliefs about medicines in patients with rheumatoid arthritis and systemic lupus erythematosus: a comparison between patients of South Asian and White British origin. Rheumatology 2008; 47(5):690-697.

(56)   Kemp S, Feely M, Hay A, Wild H, Cooper C. Psychological factors and use of antiepileptic drugs: Pilot work using an objective measure of adherence. Psychology 2007; 12(1):107-113.

(57)   Aikens JE, Nease-Donald-E-Jr, Klinkman MS. Explaining patients' beliefs about the necessity and harmfulness of antidepressants. Ann Fam Med 2008; 6(1):23-29.

(58)   Clifford S, Barber N, Horne R. Understanding different beliefs held by adherers, unintentional nonadherers, and intentional nonadherers: application of the Necessity-Concerns Framework. J Psychosom Res 2008;(1):41-46.

(59)   Jenkins L, Britten N, Stevenson F, Barber N, Bradley C. Developing and using quantitative instruments for measuring doctor-patient communication about drugs. Patient Educ Couns 2003; 50(3):273-278.

(60)   Theunissen NCM. Manipulation of patient-provider interaction: Discussing illness representations or action plans concerning adherence. Patient Educ Couns 2003; 51(3):247-258.

(61)   Strydom A, Forster M, Wilkie BM, Edwards C, Hall IS. Patient information leaflets for people with learning disabilities who take psychiatric medication. Br J Learn Disabil 2001; 29(2):72-76.

(62)   Agård A, Hermerén G, Herlitz J. When is a patient with heart failure adequately informed? A study of patients' knowledge of and attitudes toward medical information. Heart Lung 2004; 33(4):219-226.

(63)   Duggan C, Bates I. Development and evaluation of a survey tool to explore patients' perceptions of their prescribed drugs and their need for drug information. Int J Pharm Pract 2000; 8(1):42-52.

(64)   Astrom K, Carlsson J, Bates I, Webb DG, Duggan C, Sanghani P et al. Desire for information about drugs. A multi-method study in general medical inpatients. Pharm World Sci 2000; 22(4):159-164.

(65)   Zwaenepoel L, Bilo R, De BW, De VM, Reyntens J, Hoorens V et al. Desire for information about drugs: a survey of the need for information in psychiatric in-patients. Pharm World Sci 2005; 27(1):47-53.

(66)   Trevena LJ, Davey HM, Barratt A, Butow P, Caldwell P. A systematic review on communicating with patients about evidence. J Eval Clin Pract 2006; 12(1):13-23.

(67)   Wills CE, Holmes RM. Patient comprehension of information for shared treatment decision making: state of the art and future directions. Patient Educ Couns 2003; 50(3):285-290.

(68)   Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K et al. A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines. Health Technol Assess 2007; 11(5):1-98.

(69)   O'Connor AM, Stacey D, Entwistle V, Llewellyn-Thomas H, Rovner D, Holmes-Rovner M et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2003;(CD001431).

(70)   Montgomery AA, Fahey T, Peters TJ. A factorial randomised controlled trial of decision analysis and an information video plus leaflet for newly diagnosed hypertensive patients. Br J Gen Pract 2003; 53(491):446-453.

(71)   Weymiller AJ, Montori VM, Jones LA, Gafni A, Guyatt GH, Bryant SC et al. Helping patients with type 2 diabetes mellitus make treatment decisions: statin choice randomized trial. Arch Intern Med 2007; 167(10):1076-1082.

(72)   Thomson RG, Eccles MP, Steen IN, Greenaway J, Stobbart L, Murtagh MJ et al. A patient decision aid to support shared decision-making on anti-thrombotic treatment of patients with atrial fibrillation: randomised controlled trial. Qual Saf Health Care 2007; 16(3):216-223.

(73)   Oakley S, Walley T. A pilot study assessing the effectiveness of a decision aid on patient adherence with oral bisphosphonate medication. Pharm J 2006; 276(7399):536-538.

(74)   Fraenkel L, Rabidou N, Wittink D, Fried T. Improving informed decision-making for patients with knee pain. J Rheumatol 2007; 34(9):1894-1898.

(75)   Hamann J, Cohen R, Leucht S, Busch R, Kissling W. Shared decision making and long-term outcome in schizophrenia treatment. J Clin Psychiatry 2007; 68(7):992-997.

(76)   Bikowski RM, Ripsin CM, Lorraine VL. Physician-patient congruence regarding medication regimens. J Am Geriatr Soc 2001; 49(10):1353-1357.

(77)   McKinstry B, Ashcroft RE, Car J, Freeman GK, Sheikh A. Interventions for improving patients' trust in doctors and groups of doctors. Cochrane Database Syst Rev 2006;(CD004134).

(78)   van-Dam HA. Provider-patient interaction in diabetes care: effects on patient self-care and outcomes. A systematic review. Patient Educ Couns 2003; 51(1):17-28.

(79)   Edwards A, Elwyn G, Hood K, Atwell C, Robling M, Houston H et al. Patient-based outcome results from a cluster randomized trial of shared decision making skill development and use of risk communication aids in general practice. Fam Pract 2004; 21(4):347-354.

(80)   Cohen D, Longo MF, Hood K, Edwards A, Elwyn G. Resource effects of training general practitioners in risk communication skills and shared decision making competences. J Eval Clin Pract 2004; 10(3):439-445.

(81)   Savage R, Armstrong D. Effect of a general practitioner's consulting style on patients' satisfaction: a controlled study. Br Med J 1990; 301(6758):968-970.

(82)   Shields CG, Epstein RM, Fiscella K, Franks P, McCann R, McCormick K et al. Influence of accompanied encounters on patient-centeredness with older patients. J Am Board Fam Pract 2005; 18(5):344-354.

(83)   McCann S, Weinman J. Encouraging patient participation in general practice consultations: effect on consultation length and content, patient satisfaction and health. Psychol Health 1996; 11(6):857-869.

(84)   Middleton JF, McKinley RK, Gillies CL. Effect of patient completed agenda forms and doctors' education about the agenda on the outcome of consultations: randomised controlled trial. Br Med J 2006; 332(7552):1238-1242.

(85)   McLean M, Armstrong D. Eliciting patients' concerns: a randomised controlled trial of different approaches by the doctor. Br J Gen Pract 2004; 54(506):663-666.

(86)   Hamann J, Langer B, Winkler V, Busch R, Cohen R, Leucht S et al. Shared decision making for in-patients with schizophrenia. Acta Psychiatr Scand 2006; 114(4):265-273.

(87)   Brouwer WBF, Exel NJ, Berg Bvd, Bos GAM, Koopmanschap MA. Process utility from providing informal care: the benefit of caring. Health Policy 2005; 74(1):85-99.

(88)   Albus-Christian S-NS-BF. Preferences regarding medical and psychosocial support in HIV-infected patients. Patient Educ Couns 2005; 56(1):16-20.

(89)   Aristides M, Weston AR, FitzGerald P, Le RC, Maniadakis N. Patient preference and willingness-to-pay for Humalog Mix25 relative to Humulin 30/70: a multicountry application of a discrete choice experiment. Value Health 2004; 7(4):442-454.

(90)   Beusterien KM, Dziekan K, Flood E, Harding G, Jordan JC. Understanding patient preferences for HIV medications using adaptive conjoint analysis: feasibility assessment. Value Health 2005; 8(4):453-461.

(91)   Frileux S, Muñoz Sastre MT, Mullet E, Sorum PC. The impact of the preventive medical message on intention to change behavior. Patient Educ Couns 2004; 52(1):79-88.

(92)   Goldring AB, Taylor SE, Kemeny ME, Anton PA. Impact of health beliefs, quality of life, and the physician-patient relationship on the treatment intentions of inflammatory bowel disease patients. Health Psychol 2002; 21(3):219-228.

(93)   Honish A, Westerfield W, Ashby A, Momin S, Phillippi R. Health-related quality of life and treatment compliance with diabetes care. Dis Manag 2006; 9(4):195-200.

(94)   Kellett N, West F, Finlay AY. Conjoint analysis: a novel, rigorous tool for determining patient preferences for topical antibiotic treatment for acne. A randomised controlled trial. Br J Dermatol 2006; 154(3):524-532.

(95)   King MT, Hall J, Lancsar E, Fiebig D, Hossain I, Louviere J et al. Patient preferences for managing asthma: results from a discrete choice experiment. Health Econ 2007; 16:703-717.

(96)   Lamiraud K, Moatti JP. Economic implications of nonadherence to highly active antiretroviral treatment in HIV patients. Expert Opin Pharmacother 2006; 7(2):135-143.

(97)   Lancsar EJ, Hall JP, King M, Kenny P, Louviere JJ, Fiebig DG et al. Using discrete choice experiments to investigate subject preferences for preventive asthma medication. Respirology 2007; 12(1):127-136.

(98)   Mahadevia PJ, Shah S, Leibman C, Kleinman L, Dowd L. Patient preferences for sensory attributes of intranasal corticosteroids and willingness to adhere to prescribed therapy for allergic rhinitis: a conjoint analysis. Ann Allergy Asthma Immunol 2004; 93(4):345-350.

(99)   Mark TL, Swait J. Using stated preference and revealed preference modeling to evaluate prescribing decisions. Health Econ 2004; 13(6):563-573.

(100)   Reginster JY, Rabenda V, Neuprez A, Reginster JY, Rabenda V, Neuprez A. Adherence, patient preference and dosing frequency: understanding the relationship. [Review] [30 refs]. Bone 2006; 38(4 Suppl 1):S2-S6.

(101)   Richter J, Eisemann M, Zgonnikova E. Doctors' authoritarianism in end-of-life treatment decisions. A comparison between Russia, Sweden and Germany. J Med Ethics 2001; 27(3):186-191.

(102)   Ryan M, Farrar S. Using conjoint analysis to elicit preferences for health care. Br Med J 2000; 320(7248):1530-1533.

(103)   Stone VE, Jordan J, Tolson J, Miller R, Pilon T. Perspectives on adherence and simplicity for HIV-infected patients on antiretroviral therapy: self-report of the relative importance of multiple attributes of highly active antiretroviral therapy (HAART) regimens in predicting adherence. J Acquir Immune Defic Syndr 2004; 36(3):808-816.

(104)   Vick S, Scott A. Agency in health care. Examining patients' preferences for attributes of the doctor-patient relationship. J Health Econ 1998; 17(5):587-605.

(105)   Munro SA, Lewin SA, Smith HJ, Engel ME, Fretheim A, Volmink J. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Med 2007; 4(7):1230-1245.

(106)   Mills EJ, Nachega JB, Bangsberg DR, Singh S, Rachlis B, Wu P et al. Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. PLoS Med 2006; 3(11):2039-2064.

(107)   Carrick R, Mitchell A, Powell RA, Lloyd K. The quest for well-being: a qualitative study of the experience of taking antipsychotic medication. Psychol Psychother 2004; 77(1):19-33.

(108)   Deegan PE. The importance of personal medicine: a qualitative study of resilience in people with psychiatric disabilities. Scand J Public Health 2005; 33(Suppl 66):29-35.

(109)   Lewis MP, Colbert A, Erlen J, Meyers M. A qualitative study of persons who are 100% adherent to antiretroviral therapy. AIDS Care 2006; 18(2):140-148.

(110)   Cooper V, Buick D, Horne R, Lambert N, Gellaitry G, Leake H et al. Perceptions of HAART among gay men who declined a treatment offer: preliminary results from an interview-based study. AIDS Care 2002; 14(3):319-328.

(111)   Ogedegbe G, Harrison M, Robbins L, Mancuso CA, Allegrante JP. Barriers and facilitators of medication adherence in hypertensive African Americans: a qualitative study. Ethn Dis 2004; 14(1):3-12.

(112)   Lukoschek P. African Americans' beliefs and attitudes regarding hypertension and its treatment: a qualitative study. J Health Care Poor Underserved 2003; 14(4):566-587.

(113)   Wilson HS, Hutchinson SA, Holzemer WL. Reconciling incompatibilities: a grounded theory of HIV medication adherence and symptom management. Qual Health Res 2002; 12:1309-1322.

(114)   Bollini P, Tibaldi G, Testa C, Munizza C. Understanding treatment adherence in affective disorders: a qualitative study. J Psychiatr Ment Health Nurs 2004; 11(6):668-674.

(115)   Adam BD, Maticka TE, Cohen JJ. Adherence practices among people living with HIV. AIDS Care 2003; 15(2):263-274.

(116)   Scotto CJ. The lived experience of adherence for patients with heart failure. J Cardiopulm Rehabil 2005; 25(3):158-163.

(117)   Alfonso V, Bermbach N, Geller J, Montaner J-SG. Individual variability in barriers affecting people's decision to take HAART: a qualitative study identifying barriers to being on HAART. Aids Patient Care STDS 2006; 20(12):848-857.

(118)   Sidat M, Fairley C, Grierson J. Experiences and perceptions of patients with 100% adherence to highly active antiretroviral therapy: a qualitative study. Aids Patient Care STDS 2007; 21(7):509-520.

(119)   Pyne JM, McSweeney J, Kane HS, Harvey S, Bragg L, Fischer E. Agreement between patients with schizophrenia and providers on factors of antipsychotic medication adherence. Psychiatr Serv 2006; 57(8):1170-1178.

(120)   Kikkert MJ, Schene AH, Koeter-Maarten WJ, Robson D, Born A, Helm H et al. Medication adherence in schizophrenia: exploring patients', carers' and professionals' views. Schizophr Bull 2006; 32(4):786-794.

(121)   Vinter-Repalust N, Petricek G, Katic M. Obstacles which patients with type 2 diabetes meet while adhering to the therapeutic regimen in everyday life: Qualitative study. Croat Med J 2004; 45(5):630-636.

(122)   Campero L, Herrera C, Kendall T, Caballero M. Bridging the gap between antiretroviral access and adherence in Mexico. Qual Health Res 2007; 17:599-611.

(123)   Reid M, Clark A, Murdoch DL, Morrison C, Capewell S, McMurray J. Patients strategies for managing medication for chronic heart failure. Int J Cardiol 2006; 109(1):66-73.

(124)   Elliott RA, Ross DD, Adams AS, Safran DG, Soumerai SB. Strategies for coping in a complex world: adherence behavior among older adults with chronic illness. J Gen Intern Med 2007; 22(6):805-810.

(125)   Aronson B. Medication management behaviors of adherent short-term antibiotic users. Clin Excell Nurse Pract 2005; 9(1):23-30.

(126)   Garcia Popa-Lisseanu MG, Greisinger A, Richardson M, Malley KJ, Janssen NM, Marcus DM et al. Determinants of treatment adherence in ethnically diverse, economically disadvantaged patients with rheumatic disease. J Rheumatol 2005; 32(5):913-919.

(127)   Erwin J, Peters B. Treatment issues for HIV+ Africans in London. Soc Sci Med 1999; 49(11):1519-1528.

(128)   Mutchler JE, Bacigalupe G, Coppin A, Gottlieb A. Language barriers surrounding medication use among older Latinos. J Cross Cult Gerontol 2007; 22(1):101-114.

(129)   Lawton J, Ahmad N, Hallowell N, Hanna L, Douglas M. Perceptions and experiences of taking oral hypoglycaemic agents among people of Pakistani and Indian origin: qualitative study. Br Med J 2005; 330(7502):1247-1249.

(130)   Morgan M, Figueroa-Muñoz J. Barriers to uptake and adherence with malaria prophylaxis by the African community in London, England: focus group study. Ethn Health 2005; 10(4):355-372.

(131)   Ring L, Kettis LA, Kjellgren K, I, Kindell Y, Maroti M, Serup J. Living with skin diseases and topical treatment: patients' and providers' perspectives and priorities. J Dermatolog Treat 2007; 18(4):209-218.

(132)   Chen CH, Wu JR, Yen M, Chen ZC. A model of medication-taking behavior in elderly individuals with chronic disease. J Cardiovasc Nurs 2007; 22(5):359-365.

(133)   Gascón JJ, Sánchez OM, Llor B, Skidmore D, Saturno PJ. Why hypertensive patients do not comply with the treatment: results from a qualitative study. Fam Pract 2004; 21(2):125-130.

(134)   Vermeire E, Van RP, Coenen S, Wens J, Denekens J. The adherence of type 2 diabetes patients to their therapeutic regimens: A qualitative study from the patient's perspective. Pract Diabetes Int 2003; 20(6):209-214.

(135)   George M, Freedman TG, Norfleet AL, Feldman H, I, Apter AJ. Qualitative research-enhanced understanding of patients' beliefs: results of focus groups with low-income, urban, African American adults with asthma. J Allergy Clin Immunol 2003; 111(5):967-973.

(136)   Fraenkel-Liana MS. Participation in medical decision making: The patients' perspective. Med Decis Making 2007; 27(5):533-538.

(137)   Field K, Ziebland S, McPherson A, Lehman R. 'Can I come off the tablets now?' A qualitative analysis of heart failure patients' understanding of their medication. Fam Pract 2006; 23(6):624-630.

(138)   Badger F, Nolan P. Concordance with antidepressant medication in primary care. Nurs Stand 2006; 20(52):35-40.

(139)   Givens JL, Datto CJ, Ruckdeschel K, Knott K, Zubritsky C, Oslin DW et al. Older patients' aversion to antidepressants: A qualitative study. J Gen Intern Med 2006; 21(2):146-151.

(140)   Attebring MF, Herlitz J, Ekman I. Intrusion and confusion--the impact of medication and health professionals after acute myocardial infarction. Eur J Cardiovasc Nurs 2005; 4(2):153-159.

(141)   Nair KM, Levine-Mitchel AH, Lohfeld LH, Gerstein HC. I take what I think works for me: a qualitative study to explore patient perception of diabetes treatment benefits and risks. Can J Clin Pharmacol 2007; 14(2):e251-e259.

(142)   Gordon K, Smith F, Dhillon S. Effective chronic disease management: Patients' perspectives on medication-related problems. Patient Educ Couns 2007; 65(3):407-415.

(143)   Bajcar J. Task analysis of patients' medication-taking practice and the role of making sense: a grounded theory study. Res Social Adm Pharm 2006; 2(1):59-82.

(144)   Taylor SA, Galbraith SM, Mills RP. Causes of non-compliance with drug regimens in glaucoma patients: a qualitative study. J Ocul Pharmacol Ther 2002; 18(5):401-409.

(145)   Enriquez M, Lackey NR, Connor MC, McKinsey DS. Successful adherence after multiple HIV treatment failures. J Adv Nurs 2004; 45(4):438-446.

(146)   Gray J. Becoming adherent: experiences of persons living with HIV/AIDS. J Assoc Nurses AIDS Care 2006; 17(3):47-54.

(147)   Bane C, Hughes CM, Cupples ME, McElnay JC. The journey to concordance for patients with hypertension: a qualitative study in primary care. Pharm World Sci 2007; 29(5):534-540.

(148)   Hayes RP, Bowman L, Monahan PO, Marrero DG, McHorney CA. Understanding diabetes medications from the perspective of patients with type 2 diabetes: prerequisite to medication concordance. Diabetes Educ 2006; 32(3):404-414.

(149)   Mills EJ. Adherence to antiretroviral therapy in sub-saharan Africa and north America: a meta-analysis. JAMA 2006; 296(6):679-690.

(150)   Hawkshead J, Krousel-Wood MA. Techniques for measuring medication adherence in hypertensive patients in outpatient settings: advantages and limitations. Dis Manag Health Out 2007; 15(2):109-118.

(151)   Gagné CGG. Improving self-report measures of non-adherence to HIV medications. Psychol Health 2005; 20(6):803-816.

(152)   Paterson DL, Potoski B, Capitano B. Measurement of adherence to antiretroviral medications. J Acquir Immune Defic Syndr 2002; 31(Suppl 3):S103-S106.

(153)   Miller LG, Hays RD. Measuring adherence to antiretroviral medications in clinical trials. HIV Clin Trials 2000; 1(1):36-46.

(154)   Turner BJ. Adherence to antiretroviral therapy by human immunodeficiency virus-infected patients. J Infect Dis 2002; 185(Suppl 2):S143-S151.

(155)   Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther 1999; 21(6):1074-1090.

(156)   Bender B, Milgrom H, Rand C. Nonadherence in asthmatic patients: is there a solution to the problem? Ann Allergy Asthma Immunol 1997; 79(3):177-186.

(157)   La Fleur J. Methods to measure patient compliance with medication regimens. J Pain Palliat Care Pharmacother 2004; 18(3):81-87.

(158)   Rand CS, Wise RA. Measuring adherence to asthma medication regimens. Am J Respir Crit Care Med 1994; 149(2 Pt 2):S69-S76.

(159)   Hecht FM. Measuring HIV treatment adherence in clinical practice. AIDS Clin Care 1998; 10(8):57-59.

(160)   Bennett-Johnson SB. Methodological issues in diabetes research. Measuring adherence. Diabetes Care 1992; 15(11):1658-1667.

(161)   George J, Kong-David CM, Stewart K. Adherence to disease management programs in patients with COPD. Int J Chron Obstruct Pulmon Dis 2007; 2(3):253-262.

(162)   Garber MC, Nau DP, Erickson SR, Aikens JE, Lawrence JB. The concordance of self-report with other measures of medication adherence: a summary of the literature. Med Care 2004; 42(7):649-652.

(163)   Dunbar J, Dunning EJ, Dwyer K. Compliance measurement with arthritis regimen. Arthritis Care Res 1989;(3):S8-16.

(164) Medical Research Council. A framework for development and evaluation of RCTs for complex interventions to improve health. 2000.

(165) Shi L, Hudges M, Yurgin N, Boye KS. Impact of dose frequency on compliance and health outcomes: a literature review (1966-2006). Expert Rev Pharmacoeconomics Outcomes Res 2007; 7(2):187-202.

(166) Schroeder K, Fahey T, Ebrahim S. How Can We Improve Adherence to Blood Pressure-Lowering Medication in Ambulatory Care? Systematic Review of Randomized Controlled Trials. Arch Intern Med 2004; 164(7):722-732.

(167) Iskedjian M, Einarson TR, MacKeigan LD, Shear N, Addis A, Mittmann- N et al. Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: evidence from a meta-analysis. Clin Ther 2002; 24(2):302-316.

(168) Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001; 23(8):1296-1310.

(169) Baird MG, Bentley-Taylor MM, Carruthers SG, Dawson KG, Laplante LE, Larochelle P et al. A study of efficacy, tolerance and compliance of once-daily versus twice-daily metoprolol (Betaloc) in hypertension. Betaloc Compliance Canadian Cooperative Study Group. Clin Invest Med 1984; 7(2):95-102.

(170) Brown BG, Bardsley J, Poulin D, Hillger LA, Dowdy A, Maher VM et al. Moderate dose, three-drug therapy with niacin, lovastatin, and colestipol to reduce low-density lipoprotein cholesterol <100 mg/dl in patients with hyperlipidemia and coronary artery disease. Am J Cardiol 1997; 80(2):111-115.

(171) Girvin B, McDermott BJ, Johnston GD. A comparison of enalapril 20 mg once daily versus 10 mg twice daily in terms of blood

pressure lowering and patient compliance. J Hypertens 1999; 17(11):1627-1631.

(172) Portsmouth SD, Osorio J, McCormick K, Gazzard BG, Moyle GJ. Better maintained adherence on switching from twice-daily to once-daily therapy for HIV: a 24-week randomized trial of treatment simplification using stavudine prolonged-release capsules. HIV Med 2005; 6(3):185-190.

(173) Molina JM, Podsadecki TJ, Johnson MA, Wilkin A, Domingo P, Myers R et al. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. AIDS Res Hum Retroviruses 2007; 23(12):1505-1514.

(174) Claxton A, Cramer J, Pierce C. A systematic Review of the Associations Between Dose Regimens and Medication Compliance. Clin Ther 2001; 23(8):1296.

(175) Rudd P, Miller NH, Kaufman J, Kraemer HC, Bandura A, Greenwald G et al. Nurse management for hypertension. A systems approach. Am J Hypertens 2004; 17(10):921-927.

(176) Parienti JJ, Massari V, Reliquet V, Chaillot F, Le MG, Arvieux C et al. Effect of twice-daily nevirapine on adherence in HIV-1-infected patients: a randomized controlled study. AIDS 2007; 21(16):2217-2222.

(177) Hirth RA, Greer SL, Albert JM, Young EW, Piette JD. Out-of-pocket spending and medication adherence among dialysis patients in twelve countries. Health Aff 2008; 27(1):89-102.

(178) Atella V, Schafheutle E, Noyce P, Hassell K. Affordability of medicines and patients' cost-reducing behaviour: empirical evidence based on SUR estimates from Italy and the UK. Appl Health Econ Health Policy 2005; 4(1):23-35.

(179) Orton L, Barnish G. Unit-dose packaged drugs for treating malaria. [Review] [40 refs]. Cochrane Database Syst Rev 2005;(CD004614).

(180) Schneider PJ, Murphy JE, Pedersen CA. Impact of medication packaging on adherence and treatment outcomes in older ambulatory patients. J Am Pharm Assoc 2008; 48(1):58-63.

(181) Becker LA, Glanz K, Sobel E. A randomized trial of special packaging of antihypertensive medications. J Fam Pract 1986; 22(4):357-361.

(182) Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial.[see comment]. JAMA 2006; 296(21):2563-2571.

(183) Heneghan CJ, Glasziou P, Perera R. Reminder packaging for improving adherence to self-administered long-term medications. [Review] [86 refs]. Cochrane Database Syst Rev 2006;(CD005025).

(184) Henry A, Batey RG. Enhancing compliance not a prerequisite for effective eradication of Helicobacter pylori: the helP study. Am J Gastroenterol 1999; 94(3):811-815.

(185) Peterson GM, McLean S, Millingen KS. A randomised trial of strategies to improve patient compliance with anticonvulsant therapy. Epilepsia 1984; 25(4):412-417.

(186) Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med 2007; 120:713-719.

(187) Stewart A, Noakes T, Eales C, Shepard K, Becker P, Veriawa Y. Adherence to cardiovascular risk factor modification in patients with hypertension. Cardiovasc J S Afr 2005; 16(2):102-107.

(188) Urien AM, Guillen VF, Beltran DO, Pinzotas CL, Perez ER, Arocena MO et al. Telephonic back-up improves antibiotic compliance in acute tonsillitis/pharyngitis. Int J Antimicrob Agents 2004; 23(2):138-143.

(189)   Piette JD, Weinberger M, McPhee SJ, Mah CA, Kraemer FB, Crapo LM. Do automated calls with nurse follow-up improve self-care and glycemic control among vulnerable patients with diabetes? Am J Med 2000; 108(1):20-27.

(190)   Beaucage K, Lachance-Demers H, Ngo TT, Vachon C, Lamarre D, Guevin JF et al. Telephone follow-up of patients receiving antibiotic prescriptions from community pharmacies. Am J Health Syst Pharm 2006; 63(6):557-563.

(191)   Hamet P, Campbell N, Curnew G, Eastwood C, Pradhan A. Avapromise: a randomized clinical trial for increasing adherence through behavioural modification in essential hypertension. Exp Clin Cardiol 2003; 7:165-172.

(192)   Vrijens B, Belmans A, Matthys K, de K, Lesaffre E. Effect of intervention through a pharmaceutical care program on patient adherence with prescribed once-daily atorvastatin. Pharmacoepidemiol Drug Saf 2006; 15(2):115-121.

(193)   Mannheimer SB, Morse E, Matts JP, Andrews L, Child C, Schmetter B et al. Sustained benefit from a long-term antiretroviral adherence intervention: results of a large randomized clinical trial. J Acquir Immune Defic Syndr 2006; 43(SUPPL. 1):S41-S47.

(194)   Sackett DL, Gibson ES, Taylor DW. Randomised clinical trial of strategies for improving medication compliance in primary hypertension. Lancet 1975; 1(7918):1205-1207.

(195)   Guthrie RM. The effects of postal and telephone reminders on compliance with pravastatin therapy in a national registry: results of the first myocardial infarction risk reduction program. Clin Ther 2001; 23(6):970-980.

(196)   Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP. Interventions to enhance medication adherence. Cochrane Database Syst Rev 2005;(CD000011).

(197) De Geest S, Schafer-Keller P, Denhaerynck K, Thannberger N, Kofer S, Bock A et al. Supporting medication adherence in renal transplantation (SMART): a pilot RCT to improve adherence to immunosuppressive regimens. Clin Transplant 2006; 20(3):359-368.

(198) Rickles NM, Svarstad BL, Statz-Paynter JL, Taylor LV, Kobak KA. Pharmacist telemonitoring of antidepressant use: effects on pharmacist-patient collaboration. J Am Pharm Assoc 2005; 45(3):344-353.

(199) Collier AC, Ribaudo H, Mukherjee AL, Feinberg J, Fischl MA, Chesney M et al. A randomized study of serial telephone call support to increase adherence and thereby improve virologic outcome in persons initiating antiretroviral therapy. J Infect Dis 2005; 192(8):1398-1406.

(200) Kemp R, Kirov G, Everitt B, Hayward P, David A. Randomized controlled trial of compliance therapy. 18 month follow up. Br J Psychiatry 1998; 172:413-419.

(201) Rathbun RC, Farmer KC, Stephens JR, Lockhart SM. Impact of an adherence clinic on behavioral outcomes and virologic response in treatment of HIV infection: a prospective, randomized, controlled pilot study. Clin Ther 2005; 27(2):199-209.

(202) Chaplin R, Kent A. Informing patients about tardive dyskinesia. Controlled trial of patient education. Br J Psychiatry 1998; 172(Jan):78-81.

(203) Canto-De-Cetina TE, Canto P, Ordoñez LM. Effect of counseling to improve compliance in Mexican women receiving depot-medroxyprogesterone acetate. Contraception 2001; 63(3):143-146.

(204) Tuldrà A, Fumaz CR, Ferrer MJ, Bayés R, Arnó A, Balagué M et al. Prospective randomized two-arm controlled study to determine the efficacy of a specific intervention to improve long-term adherence to highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2000; 25(3):221-228.

(205) Peveler R, George C, Kinmonth AL, Campbell M, Thompson C. Effect of antidepressant drug counselling and information leaflets on

adherence to drug treatment in primary care: randomised controlled trial. Br Med J 1999; 319(7210):612-615.

(206)   Howland JS, Baker MG, Poe T. Does patient education cause side effects? A controlled trial. J Fam Pract 1990; 31(1):62-64.

(207)   Vivian EM. Improving blood pressure control in a pharmacist-managed hypertension clinic. Pharmacotherapy 2002; 22(12):1533-1540.

(208)   Finley PR, Rens HR, Pont JT, Gess SL, Louie C, Bull SA et al. Impact of a collaborative care model on depression in a primary care setting: a randomized controlled trial. Pharmacotherapy 2003; 23(9):1175-1185.

(209)   Katon W, Russo J, Von KM, Lin E, Simon G, Bush T et al. Long-term effects of a collaborative care intervention in persistently depressed primary care patients. J Gen Intern Med 2002; 17(10):741-748.

(210)   Chisholm MA, Mulloy LL, Jagadeesan M, DiPiro JT. Impact of clinical pharmacy services on renal transplant patients' compliance with immunosuppressive medications. Clin Transplant 2001; 15(5):330-336.

(211)   Adler DA, Bungay KM, Wilson IB, Pei Y, Supran S, Peckham E et al. The impact of a pharmacist intervention on 6-month outcomes in depressed primary care patients. Gen Hosp Psychiatry 2004; 26(3):199-209.

(212)   Schaffer SD, Tian L. Promoting adherence: effects of theory-based asthma education. Clin Nurs Res 2004; 13(1):69-89.

(213)   Segador J, Gil-Guillen VF, Orozco D, Quirce F, Carratala MC, Fernandez-Parker A et al. The effect of written information on adherence to antibiotic treatment in acute sore throat. Int J Antimicrob Agents 2005; 26(1):56-61.

(214)   Atherton-Naji A, Hamilton R, Riddle W, Naji S. Improving adherence to antidepressant drug treatment in primary care: a feasibility study for a randomized controlled trial of education intervention. Prim Care Psychiatr 2001; 7(2):61-67.

(215)   Gray R, Leese M, Bindman J, Becker T, Burti L, David A et al. Adherence therapy for people with schizophrenia: European multicentre randomised controlled trial. Br J Psychiatry 2006; 189(DEC.):508-514.

(216)   Wyatt GE, Longshore D, Chin D, Carmona JV, Loeb TB, Myers HF et al. The efficacy of an integrated risk reduction intervention for HIV-positive women with child sexual abuse histories. AIDS Behav 2004; 8(4):453-462.

(217)   Bechdolf A, Knost B, Kuntermann C, Schiller S, Klosterkötter J, Hambrecht M et al. A randomized comparison of group cognitive-behavioural therapy and group psychoeducation in patients with schizophrenia. Acta Psychiatr Scand 2004; 110(1):21-28.

(218)   Bechdolf A, Köhn D, Knost B, Pukrop R, Klosterkötter J. A randomized comparison of group cognitive-behavioural therapy and group psychoeducation in acute patients with schizophrenia: Outcome at 24 months. Acta Psychiatr Scand 2005; 112(3):173-179.

(219)   Weber R, Christen L, Christen S, Tschopp S, Znoj H, Schneider C et al. Effect of individual cognitive behaviour intervention on adherence to antiretroviral therapy: prospective randomized trial. Antivir Ther 2004; 9(1):85-95.

(220)   Antoni MH, Carrico AW, Duran RE, Spitzer S, Penedo F, Ironson G et al. Randomized clinical trial of cognitive behavioral stress management on human immunodeficiency virus viral load in gay men treated with highly active antiretroviral therapy. Psychosom Med 2006; 68(1):143-151.

(221)   Wagner GJ, Kanouse DE, Golinelli D, Miller LG, Daar ES, Witt MD et al. Cognitive-behavioral intervention to enhance adherence to antiretroviral therapy: a randomized controlled trial (CCTG 578). AIDS 2006; 20(9).

(222)   Lam DH, Watkins ER, Hayward P, Bright J, Wright K, Kerr N et al. A randomized controlled study of cognitive therapy for relapse prevention

for bipolar affective disorder: outcome of the first year. Arch Gen Psychiatry 2003; 60(2):145-152.

(223)   Strang JS, Falloon I-RH, Moss HB. The effects of family therapy on treatment compliance in schizophrenia. Psychopharmacol Bull 1981; 17:87-88.

(224)   Xiong W, Phillips MR, Hu X, Wang R, Dai Q, Kleinman J et al. Family-based intervention for schizophrenic patients in China. A randomised controlled trial. Br J Psychiatry 1994; 165(2):239-247.

(225)   Zhang M, Wang M, Li J, Phillips MR. Randomised-control trial of family intervention for 78 first-episode male schizophrenic patients. An 18-month study in Suzhou, Jiangsu. Br J Psychiatry Suppl 1994; 165(Suppl 24):96-102.

(226)   Miklowitz DJ, George EL, Richards JA, Simoneau TL, Suddath RL. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. Arch Gen Psychiatry 2003; 60(9):904-912.

(227)   Razali SM, Hasanah C, I, Khan UA, Subramaniam M. Psychosocial interventions for schizophrenia. J Ment Health 2000; 9(3):283-289.

(228)   Remien RH, Stirratt MJ, Dolezal C, Dognin JS, Wagner GJ, Carballo-Dieguez A et al. Couple-focused support to improve HIV medication adherence: a randomized controlled trial. AIDS 2005; 19(8):807-814.

(229)   Ruskin PE, Silver-Aylaian M, Kling MA, Reed SA, Bradham DD, Hebel JR et al. Treatment outcomes in depression: comparison of remote treatment through telepsychiatry to in-person treatment. Am J Psychiatry 2004; 161(8):1471-1476.

(230)   Kemp R, Hayward P, Applewhaite G, Everitt B, David A. Compliance therapy in psychotic patients: randomised controlled trial. Br Med J 1996; 312(7027):345-349.

(231)   O'Donnell C, Donohoe G, Sharkey L, Owens N, Migone M, Harries R et al. Compliance therapy: a randomised controlled trial in schizophrenia. Br Med J 2003; 327(7419):834-837.

(232)   Pradier C, Bentz L, Spire B, Tourette TC, Morin M, Souville M et al. Efficacy of an educational and counseling intervention on adherence to highly active antiretroviral therapy: French prospective controlled study. HIV Clin Trials 2003; 4(2):121-131.

(233)   van Servellen G, Nyamathi A, Carpio F, Pearce D, Garcia-Teague L, Herrera G et al. Effects of a treatment adherence enhancement program on health literacy, patient-provider relationships, and adherence to HAART among low-income HIV-positive Spanish-speaking Latinos. Aids Patient Care STDS 2005; 19(11):745-759.

(234)   Bosch-Capblanch X, Abba K, Prictor M, Garner P. Contracts between patients and healthcare practitioners for improving patients' adherence to treatment, prevention and health promotion activities. Cochrane Database Syst Rev 2007;(CD004808).

(235)   Haynes RB, Sackett DL, Gibson ES. Improvement of medication compliance in uncontrolled hypertension. Lancet 1976; 1(7972):1265-1268.

(236)   Sadik A, Yousif M, McElnay JC. Pharmaceutical care of patients with heart failure. Br J Clin Pharmacol 2005; 60(2):183-193.

(237)   Tsuyuki RT, Fradette M, Johnson JA, Bungard TJ, Eurich DT, Ashton T et al. A multicenter disease management program for hospitalized patients with heart failure.[see comment]. J Card Fail 2004; 10(6):473-480.

(238)   Bailey WC, Richards-Jr JM, Brooks CM, Soong S, Windsor RA, Manzella BA. A randomized trial to improve self-management practices of adults with asthma. Arch Intern Med 1990; 150(8):1664-1668.

(239)   Coté J, Cartier A, Robichaud P, Boutin H, Malo JL, Rouleau M et al. Influence on asthma morbidity of asthma education programs based on

self-management plans following treatment optimization. Am J Respir Crit Care Med 1997; 155(5):1509-1514.

(240)   Côté J, Bowie DM, Robichaud P, Parent JG, Battisti L, Boulet LP. Evaluation of two different educational interventions for adult patients consulting with an acute asthma exacerbation. Am J Respir Crit Care Med 2001; 163(6):1415-1419.

(241)   Friedman RH, Kazis LE, Jette A, Smith MB, Stollerman J, Torgerson J et al. A telecommunications system for monitoring and counseling patients with hypertension. Impact on medication adherence and blood pressure control. Am J Hypertens 1996; 9(4):285-292.

(242)   Johnson AL, Taylor DW, Sackett DL. Self-recording of blood pressure in the management of hypertension. Can Med Assoc J 1978; 119(9):1034-1039.

(243)   Morice AH, Wrench C. The role of the asthma nurse in treatment compliance and self- management following hospital admission. Respir Med 2001; 95(11):851-856.

(244)   Bailey WC, Kohler CL, Richards JM, Jr., Windsor RA, Brooks CM, Gerald LB et al. Asthma self-management: do patient education programs always have an impact? Arch Intern Med 1999; 159(20):2422-2428.

(245)   Cote J, Bowie DM, Robichaud P, Parent JG, Battisti L, Boulet LP. Evaluation of two different educational interventions for adult patients consulting with an acute asthma exacerbation. Am J Respir Crit Care Med 2001; 163(6):1415-1419.

(246)   Levy ML, Robb M, Allen J, Doherty C, Bland JM, Winter RJD. A randomized controlled evaluation of specialist nurse education following accident and emergency department attendance for acute asthma. Respir Med 2000; 94:900-908.

(247)   Marquez-Contreras E, Martell-Claros N, Gil-Guillen V, de IV, Casado-Martinez JJ, Martin-de P et al. Efficacy of a home blood pressure

monitoring programme on therapeutic compliance in hypertension: the EAPACUM-HTA study. J Hypertens 2006; 24(1):169-175.

(248) Lowe CJ, Raynor DK, Purvis J, Farrin A, Hudson J. Effects of a medicine review and education programme for older people in general practice. Br J Clin Pharmacol 2000; 50(2):172-175.

(249) Sturgess IK, McElnay JC, Hughes CM, Crealey G. Community pharmacy based provision of pharmaceutical care to older patients. Pharm World Sci 2003; 25(5):218-226.

(250) Bernsten C, Bjorkman I, Caramona M, Crealey G, Frokjaer B, Grundberger E et al. Improving the well-being of elderly patients via community pharmacy-based provision of pharmaceutical care. Drugs Aging 2001; 18(1):63-77.

(251) Begley S, Livingstone C, Hodges N, Williamson V. Impact of domiciliary pharmacy visits on medication management in an elderly population. Int J Pharm Pract 1997; 5(3):111-121.

(252) Nazareth I, Burton A, Shulman S, Smith P, Haines A, Timberal H. A pharmacy discharge plan for hospitalized elderly patients-a randomized controlled trial. Age Ageing 2001; 30(1):33-40.

(253) Lipton HL, Bird JA. The impact of clinical pharmacists' consultations on geriatric patients' compliance and medical care use: a randomized controlled trial. Gerontologist 1994; 34(3):307-315.

(254) Hanlon JT, Weinberger M, Samsa GP, Schmader KE, Uttech KM, Lewis IK et al. A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. Am J Med 1996; 100(4):428-437.

(255) Taylor CT, Byrd DC, Krueger K. Improving primary care in rural Alabama with a pharmacy initiative. Am J Health Syst Pharm 2003; 60(11):1123-1129.

(256) Grymonpre RE, Williamson DA, Montgomery PR. Impact of a pharmaceutical care model for non-institutionalised elderly: results of a randomised, controlled trial. Int J Pharm Pract 2001; 9(4):235-241.

(257) Sookaneknun P, Richards RM, Sanguansermsri J, Teerasut C. Pharmacist involvement in primary care improves hypertensive patient clinical outcomes. Ann Pharmacother 2004; 38(12):2023-2028.

(258) Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freemantle N, Vail A. Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial. Health Technol Assess 2002; 6(20):1-86.

(259) Elliott RA, Barber N, Horne R. Cost-effectiveness of adherence-enhancing interventions: a quality assessment of the evidence. Ann Pharmacother 2005; 39(3):508-515.

(260) Urquhart J. Patient non-compliance with drug regimens: measurement, clinical correlates, economic impact. Eur Heart J 1996; 17 Suppl A:8-15.

(261) Girvin BG, Johnston GD. Comparison of the effects of a 7-day period of non-compliance on blood pressure control using three different antihypertensive agents. J Hypertens 2004; 22(7):1409-1414.

(262) Cleemput I, Kesteloot K, DeGeest S. A review of the literature on the economics of noncompliance: room for methodological improvement. Health Policy 2002; 59(1):65-94.

(263) Hughes DA, Bagust A, Haycox A, Walley T. The impact of non-compliance on the cost-effectiveness of pharmaceuticals: a review of the literature. [Review] [52 refs]. Health Econ 2001; 10(7):601-615.

(264) Bosmans JE, Brook OH, Van-Hout H-PJ, De-Bruijne MC, Nieuwenhuyse- H, Bouter LM et al. Cost effectiveness of a pharmacy-based coaching programme to improve adherence to antidepressants. Pharmacoeconomics 2007; 25(1):25-37.

(265) Cleemput I, Kesteloot K, Vanrenterghem Y, De GS. The economic implications of non-adherence after renal transplantation. Pharmacoeconomics 2004; 22(18):1217-1234.

(266) Brunenberg DEM, Wetzels GEC, Nelemans PJ, Dirksen CD, Severens JL, Stoffers HEJH et al. Cost effectiveness of an adherence-improving programme in hypertensive patients. Pharmacoeconomics 2007; 25(3):239-251.

(267) Edwards NC, Locklear JC, Rupnow MF, Diamond RJ. Cost effectiveness of long-acting risperidone injection versus alternative antipsychotic agents in patients with schizophrenia in the USA. Pharmacoeconomics 2005; 23(Suppl 1):75-89.

(268) Munakata J, Benner JS, Becker S, Dezii CM, Hazard EH, Tierce JC et al. Clinical and economic outcomes of nonadherence to highly active antiretroviral therapy in patients with human immunodeficiency virus. Med Care 2006; 44(10):893-899.