A new design for pragmatic randomised controlled trials: a 'Patient Cohort' RCT of treatment by a homeopath for menopausal hot flushes

Clare Relton, School of Health and Related Research,

University of Sheffield

PhD Thesis, April 2009

Abstract

There is debate regarding the effectiveness of homeopathy and its continuing provision in the NHS, and despite 150+ clinical trials there are conflicting opinions as to what can be concluded from these trials.

This thesis addresses the question: *"What type of clinical trial design can provide the information needed to make decisions about the provision of homeopathy in a publicly funded healthcare system?"*

A critique of the methods used in existing clinical trial designs was undertaken which identified twelve key criteria for appropriate clinical trial design; methods from existing standard and alternative clinical trial designs were adapted in order to derive a new clinical trial design that has the potential to meet all twelve key criteria (the 'Patient Cohort' RCT design).

A current clinical question was identified: *'What is the clinical & cost effectiveness of treatment by a homeopath for women with menopausal hot flushes?"* and a population based survey confirmed the importance of this question. The 'Patient Cohort' RCT design was piloted in an NHS setting in order to address this current clinical question.

Seventy 'with need' women were recruited to the Hot Flush Cohort of whom forty-eight were eligible for the treatment, a proportion of whom were randomly selected to be offered the treatment. 70.8% of those offered treatment accepted the offer and completion of outcome measures was high (93.7%). The results indicate that a full trial of this treatment for this condition may be worthwhile conducting.

A full RCT using this design would be an appropriate clinical trial design to provide answers as to the provision of homeopathy and other clinician delivered interventions in publicly funded healthcare system such as the NHS. The 'Patient Cohort' RCT design can be usefully applied to clinical questions that require very pragmatic approaches yet need the scientific rigour of randomisation.

Chapter 1 Introduction

1.1   The need for clinical trials

Worldwide, publicly funded healthcare systems spend vast amounts of money on healthcare with the world's largest publicly funded health service (the UK's National Health Service) spending an estimated £98.6 billion for 2008-9 (HM Treasury 2008). Principal fund holders in the NHS are urged to commission healthcare which has the '*best evidence'* (Sackett et al., 2000a) and advocate that patients should receive treatments which are supported by the most scientifically valid medical research and that evidence from clinical trials and systematic reviews of clinical trials are the highest ranked scientific evidence (Sackett et al., 2000a). Central to this search for the *best evidence* is the conduct of clinical trials to provide answers to questions which will allow more effective healthcare. Information from clinical trials is required by the publicly funded healthcare systems such as the NHS and the question of the most appropriate clinical trial design is thus an important question.

1.2   Clinical trials and their design

1.2.1   Definitions

A clinical trial is defined in the Dictionary of Epidemiology (Last, 2001) as a '*research activity that involves the administration of a test regimen to humans to evaluate its efficacy and safety'*. Clinical trials are also sometimes called 'interventional studies' in order to differentiate them from observational studies where the researchers do not actively manage the experiment. Medical Subject Headings (MeSH) Terms are the United States National Library of Medicines controlled vocabulary used for indexing articles on MEDLINE/PubMed. MeSH terminology provides a consistent way to retrieve information that may use different terminology for the same concepts (http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh accessed 2.6.08)
The MeSH definition of 'clinical trial' is:

> *"Pre-planned studies of the safety, efficacy, or optimum dosage schedule (if appropriate) of one or more diagnostic, therapeutic, or prophylactic drugs, devices, or*

techniques selected according to predetermined criteria of eligibility and observed for
predefined evidence of favorable and unfavorable effects".

1.2.2 Types of trials

There are many different types of trials and different ways of classifying and describing trials. A trial can be a controlled trial or a randomised controlled[1] trial (RCT). An RCT is where groups have been formed through random allocation (Torgerson & Torgerson, 2008). The limitation of randomisation is that it is a method based on probability, and therefore one cannot assume that simply because randomisation has been used, that the groups being compared do not differ in terms of any baseline differences which could confound the interpretation of the trial results. However, the strength of the RCT is that by randomisation, assuming adequate concealment of group allocation, the distribution of any known or unknown prognostic factors at baseline arises purely by chance, thus randomisation is the main method that ensures that allocation bias is eliminated at baseline (Torgerson & Torgerson, 2008).

1.2.3 Purposes of trials

Clinical trials are often described in terms of drug therapy, but they can be used to assess any aspect of healthcare. The purpose of a clinical trial can be to identify one or more of the following aspects of any type of healthcare: safety, adverse reactions, mode of action, specific pharmacological effect, optimum dose schedule, efficacy, effects of long term use, cost effectiveness, compliance, acceptability etc. Efficacy is the extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under 'ideal conditions'. Ideally, the determination of efficacy is based on the results of a randomised controlled trial (RCT) (Last, 2001).

1.2.4 Explanatory trials

It can be seen that there are many different types of clinical trial designs, yet the double blind randomised controlled trial has generally been regarded by many as the 'gold standard' of clinical trial designs; this type of trial is used to estimate the efficacy of an intervention. In such a trial, the intervention is compared to placebo control and neither the investigator nor the subjects know which treatment is being assigned to whom and the assignments are randomised. These types of trials are also known as 'explanatory' trials – they explain whether an intervention is efficacious, i.e. whether it can have a beneficial effect in an ideal situation.

> *'An explanatory study is a study whose main objective is to explain rather than merely*
> *describe a situation by isolating the effects of specific variables and understanding the*
> *mechanisms of action' (Last, 2001, p66).*

Most healthcare trials are explanatory or mechanistic studies (Torgerson & Torgerson, 2008).

---

[1] The term 'controlled' refers to the persons in a comparison group that differs in allocation to a regimen from the subjects of the study (Last, 2001).

1.2.5   Pragmatic trials

However, evidence from explanatory trials is uninformative about a range of implementation issues and policy questions e.g. under what conditions the outcomes of the trial can be replicated, whether the interventions are safe, effective and acceptable in routine practice. Thus the need to estimate the *'effectiveness'* of an intervention in real world clinical practice has given rise to an interest in practice based evidence from either non randomised studies (observational studies) or pragmatic randomised controlled trials. The term pragmatic was first applied to clinical trials by Schwartz & Lellouch (1967) whose seminal work made the distinction between explanatory trials (which aim to further knowledge as to how and why) and pragmatic/practical trials (which aim to inform healthcare decisions within routine practice). The Dictionary of Epidemiology defines a pragmatic study as a study whose aim is to:

> *"improve health status or health care of a specified population, provide a basis for decisions about health care, or evaluate previous actions" (Last, 2001, p140).*

1.2.6   Publicly funded healthcare systems and clinical trials

The primary audience for this thesis is publicly funded healthcare systems. A publicly funded healthcare system is not a single entity or audience, but is made up of many different perspectives. The purpose of this thesis is to search for an appropriate clinical trial design, and this search is examined from a variety of perspectives within a healthcare system (Section 1.9.2). This thesis has taken the UK National Health Service (NHS) as an example of a publicly funded healthcare system and explored the question of appropriate clinical trial design within the context of the NHS. However the questions and answers will be applicable in varying degrees to all publicly funded healthcare systems.

1.2.7   The NHS and clinical trials

Clinical trials are designed and conducted to maximise the chance of societal benefit although they are made up of treatments normally intended to be for individual benefit. In the UK, the Department of Health (DH) and its partners have spent many millions of pounds on research regarding the design, methods, operational aspects and evaluation of clinical trials. For example, the DH funded Health Technology Assessment (HTA) Methodology programme has to date funded 44 projects with an estimated total cost of £5.4 million (www.pcpoh.bham.ac.uk/publichealth/nccrm/Portfolio.htm accessed 24.4.08).

Two DH funded sources which the NHS uses to help deliver the best care are The National Institute for Health and Clinical Excellence (NICE) and the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme. The National Institute for Health and Clinical Excellence (NICE) was set up in 1999 as a special health authority in the NHS. NICE publishes clinical appraisals of particular treatments for the NHS. These appraisals are based primarily on cost effectiveness and use data primarily from clinical trials. Whereas NICE assesses and evaluates the clinical research information that already exists, there are several organisations which fund research into the best methods for producing and evaluating

clinical research information. In England this was the Health Technology Assessment Methodology programme, but this programme, now renamed the Methodology Research Programme, is supported by the Medical Research Council (MRC) and has the aim of supporting the development of methodological tools and theories to underpin health research (www.mrc.ac.uk/ApplyingforaGrant/CallsforProposals).

1.3   Homeopathy

Homeopathy is currently provided in several publicly funded healthcare systems (UK, Holland, Germany, France, Brazil) and in the UK has been provided in the NHS since its inception in 1948. Homeopathy is defined by the US National Library of Medicine as a:

> *"A system of therapeutics founded by Samuel Hahnemann (1755-1843), based on the Law of Similars where "like cures like". Diseases are treated by highly diluted substances that cause, in healthy persons, symptoms like those of the disease to be treated. The dilutions are repeated so many times that there is less than one molecule per dose and it is suggested that benefit is from the energetic life force of the original substance." (http://www.nlm.nih.gov/cgi/mesh/ accessed 1.10.07).*

Homeopathy can be delivered in two ways – either by buying over the counter homeopathic remedies or by consulting a homeopath who then prescribes individualised homeopathic remedies. There are two ongoing and sometimes intertwined debates about homeopathy – the efficacy of homeopathic remedies, and the effectiveness and cost effectiveness of the provision of homeopathy.

1.3.1   Debate about homeopathy

The efficacy of homeopathic remedies has been a topic of debate since the inception of homeopathy in 1792 and which is still ongoing e.g. currently contradictory conclusions are drawn from the same five meta-analyses of clinical trial evidence of homeopathy (Fisher, 2008; Goldacre, 2008). In reference to a comparative meta-analysis of homeopathy and allopathy which examined clinical trials of homeopathic remedies (Shang et al., 2005), the editorial of a leading medical journal stated that: *"Now doctors need to be bold and honest with their patients about homoeopathy's lack of benefit." (Horton, 2005)*[2]

1.3.2   Homeopathy and clinical trials

---

[2] The meta-analysis results change sensitively to the chosen threshold defining large sample sizes thus the results and conclusions are less definite than had been presented (Lütdke & Rutten, 2008). Others have suggested that the results are post hoc rationalisations and that its publication was a result of a breakdown of peer review and standards (Frass, 2005).

Homeopathy has its own tradition of empirical research which represents practice relevant research (provings, evaluations of reactions). Discussions as to clinical trial design for homeopathy are not a new phenomena, as clinical trial design and homeopathy trial design are inextricably linked with the first placebo clinical trials conducted in homeopathic medicines as early as 1829 when bread pills and lactose powders were prescribed as placebos in St Petersburg (Dean, 2004).

Currently homeopathy (and complementary and alternative medicine) researchers have a particular interest in driving debate about how best to evaluate complex healthcare systems as they struggle with demands to meet the standards of evidence based medicine (Boon et al., 2006). In the UK there is a growing realization that if questions as to the validity of NHS provision of homeopathy are to be answered then pragmatic trials of homeopathy are needed.

> *"Many clinicians are clear that they can now see a role for homeopathy, even if it does perform no better than placebo. I would hope that homeopaths might now divert their attention to performing randomised controlled (albeit unblinded) trials comparing 'visiting a homeopathy clinic' against "general practitioner's treatment as usual", since this might be the clinical question of more interest to patients i.e. not "do the pills work better than placebo" but "will the experience of visiting a homeopath help me feel better" (Goldacre, 2008)*

1.4   Health Services Research

This thesis is situated within the academic discipline of Health Services Research (HSR), a relatively new discipline which has been evolving since its introduction in the late 1980s in the UK, USA and Canada (Black, 1997). The most widely used definition of HSR comes from the American Academy for Health Services Research and Health Policy:

> *"Health services research is the multidisciplinary field of scientific investigation that studies how social factors, financing systems, organisational structures and processes, health technologies, and personal behaviours affect access to health care, the quality and cost of health care, and ultimately our health and well-being. Its research domains are individuals, families, organizations, institutions, communities, and populations." (Academy Health, 2002)*

Early HSR was performed by clinicians, economists, and other social scientists who developed an interest in the field. HSR currently draws on and uses a wide range of methods from many disciplines (Black, 1997) including sociology, economics, statistics, epidemiology, psychology, history, biology, medicine, nursing, biostatistics, clinical sciences and political science.

1.5   Reflexivity and bias

The concept of reflexivity has been well known in sociology and anthropology, and has entered the domain of HSR with the rise of interest in qualitative research methods. Reflexivity means:

'the sensitivity to the ways in which the researcher and the research process have shaped the data collected, including the role of prior assumptions and experience, which can influence even the most avowedly inductive enquiries' (Mays & Pope, 2000). Researchers should make their personal and intellectual biases plain at the outset of any research reports to enhance the credibility of their findings (Mays & Pope, 2000) regardless of the methods used i.e. qualitative, quantitative, or type of research i.e. primary research, secondary research.

In this context the term bias is used to describe a tendency or a preference towards a particular perspective, ideology or result. Thus in the reporting of clinical trials the investigators are urged to reveal any hidden biases by being upfront, explicit and transparent as possible about their motivations for choosing to carry out the research, the methods used, the outcomes looked for as well as the outcomes found (Jadad, 2007). Jadad lists over 60 types of bias, many of which are overtly controlled for in the research designs used, the peer review processes through which research must pass, and in the reporting standards for the publication of research such as clinical trials. However Jadad includes a number of biases (particularly in the planning phase of research) that are not overtly controlled for in any way such as: 'hidden agenda bias', 'vested interest bias', 'self fulfilling prophecy bias', 'cost and convenience bias', 'funding availability bias', 'secondary gains bias'.

Bias may have affected this thesis, thus I deal with this by describing my work biography which has considerably influenced the nature and direction of my research; in fact it would be true to say that my work biography is the source of the nature and direction of my research. The following sections describe my biases, beliefs and agendas as they relate to the research conducted for this thesis and as such can be viewed as an exercise in personal reflexivity.

1.6   My work biography

1.6.1   A homeopath

I have been a clinician for fourteen years (and still am) who practises the therapeutic modality of homeopathy. I trained at a private homeopathy college for four years part time; I have never practised any other form of medicine and am not medically qualified to practice conventional medicine. Thus my experiences as a healthcare professional have been completely within the therapeutic system of homeopathy. I have always worked in private practice treating patients with a wide variety of acute and chronic conditions in much the same way as a General Practitioner. For over 8 years (1998-2006) I also worked as a homeopath in an NHS Community clinic specialising in treating women with menopausal and pre-menstrual syndrome (PMS) problems. I arrived in the world of academia and the discipline of Health Services Research in the autumn of 2003.

1.6.2 A homeopath delivering routine healthcare

As a homeopath (and user of homeopathy) I have an *a priori* belief in the intrinsic effectiveness of all aspects of the therapeutic system of homeopathy – the homeopathic remedies, the principles of homeopathy and the effectiveness of having homeopathic treatment by consulting a trained and qualified homeopath. Alongside this belief is an aspiration for the provision of homeopathy in the NHS to be increased. My experience of working in the Sheffield NHS Community Menopause/PMS clinic as a homeopath helped engender a belief that homeopathy has a place in the NHS and that it can fulfil an unmet need particularly for patients who could not take conventional treatment. Working in the NHS Community Menopause/PMS clinic, I was in an environment where homeopathy appeared to be viewed by those who participated in that environment (doctors, nurses, receptionists, patients) as a viable and effective treatment option for women with menopausal/PMS problems.

My research is thus highly vulnerable to what Jadad describes as 'choice of question bias' (Jadad, 1998); a type of bias that can take many forms. Thus I entered academia with a 'hidden agenda bias' as I wanted to conduct a trial not in order to answer a question, but in order to demonstrate a pre-required answer – that treatment by a homeopath in some sense 'worked'. As a homeopath I had/have 'vested interest biases' towards raising the profile of the work of homeopaths as well as the credibility of the therapeutic system of homeopathy. My research is also vulnerable to 'self fulfilling prophecy bias' (Jadad, 2007) i.e. I will only conduct research which will provide me with the type of answers that I want – that homeopaths are effective in helping improve health, that the system of homeopathy is effective, cost effective, safe etc. There are obvious secondary gains to my research (albeit indirect) in that demonstrating the effectiveness of treatment by a homeopath will improve the credibility of my first profession as a homeopath.

1.6.3 A homeopath in a double blind placebo RCT

As well as my everyday experiences treating patients with homeopathy, I also experienced 'homeopathy' in an experimental setting. During 1998 - 2000 I was one of ten homeopaths who delivered 'homeopathy' in what was seen as a gold standard clinical trial – a double blind placebo randomised controlled trial of homeopathy for patients with chronic fatigue syndrome (Weatherley-Jones et al., 2004a) conducted by the Medical Care Research Unit at the University of Sheffield. The experience of participating in this trial as a homeopath was quite dissimilar to my everyday experience of being a homeopath. When relaying my experiences of participating in this trial, the trial principal investigator (Dr Weatherley-Jones) suggested I wrote them down. On 17.10.2000 I typed a single A4 side of comments, excerpts of which are quoted in this section. I wrote that it was:

> *"Strange explaining to px (*patient*) that they have a 50% chance of receiving placebo – alters the dynamic – quite radically in some pxs – such that they decide to leave the trial and seek tx (*treatment*) where have 0% chance of receiving placebo. Perhaps important that this is discussed at the beginning rather than during or after the consultation".*

Trial patients (unlike my non trial patients) would enter my consulting room having been told various pieces of information which seemed to affect the nature of the interaction between myself and my patient. Before entering my consulting room patients had been told that they: were participating in a trial, being observed by those conducting the trial through the forms that they and their homeopath had to fill in, may be given a placebo homeopathic remedy, that the likelihood of whether or not they were given a placebo would be determined by chance, would not know during the trial whether they were taking the real or the placebo homeopathic remedy and neither would the homeopath.

There were other differences to my everyday experience of providing homeopathy. Unlike private practice, patients in the trial did not pay for their consultations with me. I was unable to give the patients their homeopathic remedy directly at the end of the consultation as was my usual practice because the homeopathic remedy or placebo was dispensed by a homeopathic pharmacy in Tunbridge Wells.

> *"Strange not be actually handing the px the rx (remedy) from our own pharmacy as usually do. I realise that the handing over the remedy can be symbolic of the acknowledgment of both parties of the need for healing, for change, and can be a part of the consultation, the healing dynamic…"*

Working within a double blind placebo trial design affected not just the first consultation but every consultation:

> *"Loss of important information used in making prescription in double blind. A pxs reaction/partial reaction/ or non reaction can be very important in deciding on the second prescription. This potentially valuable information is reduced during double blind trial"*

Some or all of these dissimilarities meant that I found myself behaving differently from how I behaved in everyday homeopathic practice. I gradually altered my practice to adapt to the 'double blind placebo RCT' situation.

The experience of being in a situation where I could only partially control what treatment (remedy) a patient received plus the:

> *"Shock at finding I was wrong – that first px received placebo not real rx. Challenge to my confidence"*

meant that I started becoming more aware of the elements in my homeopathic practice that I could manipulate - 'non homeopathic remedy' elements - as I could not manipulate whether the patient received placebo or verum.

> *"Subsequently looked much more at the larger picture, the whole interaction and its relationship to healing"*

I began to amplify the use of these 'non remedy' elements wherever possible by:

- providing more of a 'counselling' type experience for patients - a time and space in which patients could explore their health – physical, emotional, mental, social, environmental, spiritual
- communicating my intention to help the patient improve their health
- communicating the 'homeopathic' diagnosis - what I saw as the essence of the patient's health problem

- providing specific dietary, lifestyle, therapeutic advice e.g. identifying and removing certain possible allergens such as wheat and dairy foods, increasing water, exercising, stopping anti-perspirants

As well as subtly changing my behaviour, the experience of attempting to deliver homeopathy within this type of experimental setting, increased my *awareness* of the power of these 'non remedy' elements in facilitating an improvement in patient's health. The effect of attempting to deliver 'homeopathy' inside an experimental setting increased my awareness of the 'non homeopathic' remedy elements in my interaction with my patients. The experience also left me with many questions about my own practice, about the nature of treatment by a homeopath, homeopathic remedies and homeopathy, about patient's experiences in clinical trials, and about what clinical trials could actually test and prove. I was left wondering whether it was possible to design a clinical trial that could answer questions about the efficacy and effectiveness of homeopathy, yet would reflect real world clinical practice as I understood it. In many ways this thesis can be understood as a search for knowledge and understanding within the context of these two seemingly disparate experiences: 'homeopathy' in routine healthcare and 'homeopathy' within an experimental setting.

1.6.4   A homeopath funded by the DH

The funding that has enabled me to train as a health services researcher has been provided by a training fellowship awarded by the DH Research Capacity Development Programme. The year I received the award, five pre doctoral and five post doctoral fellowships were ring fenced for the field of Complementary and Alternative Medicine (CAM) and experienced CAM practitioners were targeted for the awards. My fellowship funding has been for CAM research and been provided by the DH, thus making the research relevant to the needs of the NHS seems pertinent. Due to the small amount of funding for homeopathy research in the UK, it is doubtful whether this research would have happened without this funding as research is often vulnerable to 'funding availability bias' (Jadad, 2007) – where studies tend to concentrate on questions that are more readily fundable, often for a vested or a commercial interest.

I was given £15k over four years by the DH as part of the training fellowship award to fund my research costs. This amount has been sufficient to cover my research costs and thus I do not believe my research is prey to 'cost and convenience bias' – where one studies what is convenient to study but this is debatable.

1.6.5   A homeopath in Health Services Research

During the first year of my training I completed an MSc in Health Services Research. This training emphasised the primacy of the RCT as a method of establishing a causal link between intervention and outcome. It also emphasised the superior weight given to evidence from experimental research compared to non experimental (e.g. observational studies) as was demonstrated by the focus of systematic reviews on RCTs. For the dissertation component of my MSc in Health Services Research I conducted a systematic review of homeopathy for

menopausal and PMS disorders (Relton, 2004). This review identified a disparity between the observational evidence which was associated with considerable benefit, and the experimental evidence which reported treatment effects but no evidence of beneficial effect. I was puzzled by this and decided to design and conduct research into the clinical and cost effectiveness of homeopathy for menopausal hot flushes that would replicate real world clinical practice as well as use a rigorous RCT design to assess whether there was a causal link between the observed improvement and the intervention itself.

1.7   Theoretical position

The research question underlying this thesis is *"What type of clinical trial design can provide the information needed to make decisions about the provision of homeopathy in a publicly funded healthcare system?"* I have taken an essentially pragmatic approach to this research question; identifying four key perspectives in the UK publicly funded healthcare system – the NHS - and attempting to identify what is essential or key to each perspective if a particular clinical trial design is going to work – these I have called the 'key criteria'. For the sake of brevity of I have sometimes abbreviated the underlying research question to: *"what is an appropriate clinical trial design?"*

1.7.1   Pragmatism

Pragmatism derives from the work of Pierce, James, Mead and Dewey (Creswell, 2003) with recent writers including Rorty (1990) and Patton (1990). For pragmatists knowledge claims arise out of actions, situations and consequences rather than antecedent conditions. There is a concern with applications – "what works"- and solutions to problems (Patton 1990). Pragmatism focuses attention on the research problem and then uses a variety of approaches to derive knowledge about the problem – as does the multi disciplinary field of HSR. Pragmatism is not committed to any one system of philosophy and reality but draws liberally from both quantitative and qualitative assumptions engaged in research (Creswell, 2003). Individual researchers are free to choose the methods, techniques and procedures of research that best meet their needs and purposes (Creswell, 2003). Truth is what works at the time; it is not based in a strict dualism between the mind and a reality completely independent of the mind but uses all types of data in order to provide the best understanding of a research problem (Creswell, 2003). Pragmatists agree that research always occurs in social, historical, political, and other contexts (Creswell, 2003). Pragmatists believe that we need to stop asking questions about reality and the laws of nature, as *"They would simply like to change the subject"* (Rorty, 1983). This thesis takes a pragmatic position: the research question is central and the methods used are those that best meet the needs and purposes of the research question.

1.8   Aims and objectives

This thesis addresses the question *"What type of clinical trial design can provide the information needed to make decisions about the provision of homeopathy in a publicly funded healthcare system?"*

The aim of this thesis is to identify a clinical trial design that can provide the information needed to make decisions about the provision of homeopathy in a publicly funded healthcare system. The specific objectives of the thesis are to:

- Identify the components of homeopathy that are of relevance to the assessment of homeopathy for the NHS
- Identify a clinical question of current relevance to the NHS and homeopathy
- Identify the relevant key criteria for appropriate trial design from four perspectives in NHS clinical trial design (in the context of the clinical question)
- Examine existing clinical trial designs to see if they meet the identified key criteria for appropriate trial design from each of the four perspectives
- If no existing clinical trial design exists that meets the identified key criteria, then adapt an existing design or construct an appropriate trial design to meet the identified key criteria
- Take the clinical question of current relevance to the NHS and conduct a preliminary study using an appropriate trial design
- Evaluate the pilot of an appropriate trial design
- Make recommendations as to appropriate clinical trial design for homeopathy specifically, and generally for any clinician/therapeutic delivered interventions in the NHS.

1.9   Design of thesis

This thesis employs a wide range of methods, incorporating primary as well as secondary research and takes the form of an initial methodological enquiry into appropriate clinical trial design from four perspectives on clinical trials, followed by the description and empirical test of a possible appropriate trial design.

1.9.1   Methodological enquiry
The term 'Methodology' has three possible meanings:

- a collection of methods, practices, procedures and rules used by those who work in a field
- the study of such methods
- the implementation of such methods

This thesis is a predominantly methodological thesis (in all three senses of the word) in that it firstly studies and critiques the methods, practices, procedures and rules used in UK clinical trials, secondly, produces a clinical trial design or 'methodology' – a collection of methods and procedures, and thirdly implements a preliminary study of this clinical trial design. Chapters 2 to 6 consist of a methodological enquiry which aims to identify key criteria for a clinical trial design to inform decision making regarding the provision of homeopathy in a publicly funded healthcare system.

1.9.2   Four perspectives

Appropriate clinical trial design is examined from four perspectives: the intervention (homeopathy in the NHS), the condition (hot flush treatments), the patient (in clinical trials) and the scientist (as represented by the HTA Methodology programme). It is obvious that these four perspectives arose from my clinical and research experiences in homeopathy, in an NHS Menopause/PMS community clinic, treating patients in a double blind placebo RCT of homeopathy, and in my apprenticeship in the science of Health Services Research.

1.9.3   The key criteria

For each of the four perspectives, in order to identify the key criteria by which a trial design might be deemed appropriate or not, a variety of literature was examined, research processes discussed, tacit discourses explored and critical issues identified. Chapter 2 draws out key criteria for appropriate clinical trial design by examining the intervention – homeopathy and the current NHS perspective on evidence. Chapter 3 focuses on the perspective of the condition, menopausal hot flushes, by examining the strengths and weaknesses of the existing evidence for treatments for this condition in order to identify key criteria for appropriate trial design. Chapter 4 explores the individual patient's perspective by examining the literature that relates to why patients do or do not participate in clinical trials. The Informed Consent/recruitment part of the research process is deconstructed, tacit discourses of recruitment and Informed Consent are explored and key criteria for appropriate trial design from the individual patient's perspective are identified. Chapter 5 takes the science perspective as represented by the Health Technology Assessment (HTA) Methodology programme literature on issues that relate to the external validity of clinical trial design and from this literature identifies key criteria for appropriate clinical trial design.

1.9.4   An appropriate trial design

Within the HTA Methodology programme ten clinical trial designs were identified. These ten clinical trial designs are examined to determine which best match the key criteria identified in chapters 2 – 5. Chapter 6 describes a possible appropriate trial design the 'Patient Cohort' RCT design. This design is a collection of methods which attempts to meet all twelve key criteria for appropriate trial design derived from the four perspectives on clinical trial design.

1.9.5 Empirical test of an appropriate trial design

Chapters 7 and 8 report the empirical work of the thesis and the collection of primary data. These two chapters take the 'Patient Cohort' RCT design and empirically test its suitability by using the design to answer a current clinical question *'What is the clinical and cost effectiveness of treatment by a homeopath for women with menopausal hot flushes?'* Chapter 7 reports the methods and results of the preparatory work needed in order to use this design to address this question and Chapter 8 reports a preliminary empirical test of this proposed appropriate trial design.

1.9.6 Discussion

2   Chapter 9 evaluates the 'Patient Cohort' RCT design. Chapter 10 summarises and reflects on the thesis findings, and the strengths and limitations of the thesis. The generalisability of the key criteria and the findings of the pilot and the generalisability of the design are discussed. Practical, statistical, ethical challenges to the 'Patient Cohort' RCT design are briefly explored and recommendations are made for homeopathy research and clinical RCT design.

Chapter 2

The intervention: Homeopathy in the NHS

2.1. Introduction

2.1.1 Background

Homeopathy is provided in some publicly funded healthcare systems (e.g. UK, Norway, Holland, France, Germany, India, Brazil, Mexico, United Arab Emirates, Russia). Homeopathy has been provided continuously for 60 years in the UK publicly funded healthcare system – the National Health Service (NHS) since its inception in 1948[3]. The UK Faculty of Homeopathy (http://www.trusthomeopathy.org/ accessed 7.8.08) incorporated by an Act of the Parliament in 1950 states that the public has access to homeopathy under the NHS so long as patients demand it and doctors are trained to provide it. However, in the UK there is an ongoing debate regarding the provision of homeopathy in the NHS. This chapter contributes to this debate by clarifying the use of key terms used and exploring the available evidence and discussing what conclusions can be drawn from the existing evidence. Some of the arguments in sections 2.4 – 2.6 have been published (Relton et al., 2008).

2.1.2 Aims and objectives

The main question addressed in this thesis is: *"What type of clinical trial design can provide the information needed to make decisions about the provision of homeopathy in a publicly funded healthcare system?"* Chapter 2 aims to examine this question from the perspective of the intervention, homeopathy, within the UK's publicly funded healthcare system – the NHS. The objectives of this chapter are to:

- Describe homeopathy and its use and provision in the NHS
- Outline the debate regarding the NHS provision of homeopathy
- Identify central questions in the debate from an NHS viewpoint
- Identify what aspects of homeopathy need to be evaluated from the perspective of homeopathy in the NHS
- Examine the literature that relates to how treatment by a homeopath has been modelled
- Discuss how treatment by a homeopath can be evaluated

---

[3] The five homeopathic hospitals were given a personal assurance of their continuity in the NHS by Aneurin Bevan: *"I can give that absolute guarantee because otherwise it would be an emotional mutilation which nobody could possibly defend"* (Simile, 2008)

- Identify and examine existing evidence with reference to central questions in the debate regarding the NHS provision of homeopathy
- Identify key criteria for future clinical trial design from the perspective of homeopathy in the NHS

2.2. Homeopathy and its current NHS provision and use

2.2.1 Definitions of homeopathy

There are several possible definitions of homeopathy. Given the health services research focus taken with this thesis, an appropriate definition of homeopathy to use is the MEDLINE Medical Subject Headings (MeSH) http://www.nlm.nih.gov/mesh/ accessed 30.8.08. MeSH terms were developed by the United States National Library of Medicine in order to provide a standardised way to describe diseases, symptoms, treatments, drugs etc. when indexing articles in Index Medicus and MEDLINE. The MeSH scope for 'homeopathy' is:

"A system of therapeutics founded by Samuel Hahnemann (1755-1843), based on the Law of Similars where "like cures like". Diseases are treated by highly diluted substances that cause, in healthy persons, symptoms like those of the disease to be treated. The dilutions are repeated so many times that there is less than one molecule per dose and it is suggested that benefit is from the energetic life force of the original substance." (National Library of Medicine, http://www.nlm.nih.gov/mesh/MBrowser.html accessed 1.7.07)

2.2.2 Two principles of homeopathy

Homeopathy is thus defined as a 'system of therapeutics' that uses doses of substances (known as homeopathic medicines or remedies) according to two principles: similitude and potentisation. The principle of similitude is described as '*the Law of Similars*', and the principle of potentisation is alluded to as *'the dilutions are repeated so many times that there is less than one molecule per dose and it is suggested that benefit is from the energetic life force of the original substance'.*

Principle of similitude: Homeopathic treatment is based on the premise that if a substance can cause symptoms in a healthy person, then a homeopathic 'potency' (see Principle of potentisation below) of the substance has the potential to provoke a healing response in ill people with these same symptoms, known colloquially as 'like cures like'. The principle of similitude has correspondences in conventional medicine – immunisation, radiation treatment of cancer, and the clinical studies of secondary effects of many modern pharmaceutical agents such as Ritalin, Nitroglycerine etc., (Teixeira, 1999). The principle of similitude is the central tenet of homeopathy.

Principle of potentisation: The principle of potentisation states that the more that the homeopathic remedy is diluted and succussed (vigorously shaken), the more effective or 'potent' it becomes. The most potent remedies are unlikely to contain any molecules of the original substance. The principle of potentisation is colloquially known as the 'minimum dose'. The apparent implausibility of the principle of potentisation has given rise to much scientific controversy about homeopathic treatment.

2.2.3   Homeopathic medicines or remedies

Homeopathic medicines are prepared using the principle of potentisation and applied using the principle of similitude. 'Doses' of homeopathic medicines are manufactured from a wide variety of substances (e.g. extracts from plants, animals, minerals or chemicals). Homeopathic remedies are prepared by repeatedly diluting substances with intercurrrent high energy disruptions to the solution (succussion), to very low levels. Dilutions are either of 1 in 100 (C) or 1 in 10 (X). Homeopathic remedies are available over the counter and through the NHS on an FP10 prescription by any doctor registered with the General Medical Council.

2.2.4   History of homeopathy

The therapeutic system of homeopathy was formulated by the German pharmacist and doctor Samuel Hahnemann (1755-1843) in his paper called *'New principle of how to find the remedial powers of remedies'* (Hahnemann, 1811). He claimed that the true medicine should follow the principle of similitude, a principle known to the Roman physician Galen and to Paracelsus, the German physician and natural philosopher of the Renaissance (Dean, 2004). Hahnemann gave medicinal substances to healthy volunteers and studied the symptoms which those subjects suffered (this process is known as a proving or a Homeopathic Pathogenetic Trial). Hahnemann then applied the substances in cases of illness which had a similar appearance. Hahnemann knew about the toxicity of the medicinal substances which were used in his day and sought to diminish their potentially dangerous effects by diluting them successively and shaking them vigorously between the steps of the dilution while retaining their dynamic healing properties (known as the potentisation process).

2.2.5   Current use and provision of homeopathy

Homeopathy is used by patients in every country in the world, e.g. India has an estimated 300,000 practitioners of homeopathy (Manchandra, 2000), and is formally provided in many publicly funded healthcare systems. Population based research conducted in the UK in 1998 estimated that there were 470,000 users of homeopathy (Thomas et al., 2001).

Use of homeopathy in the UK

Homeopathy is provided in the UK in two ways: over the counter (OTC) purchasing of homeopathic remedies, and by practitioners of homeopathy, known as 'homeopaths'. Homeopathic remedies can be purchased OTC in pharmacies, supermarkets, health food shops or can be ordered directly from homeopathic pharmacies. A UK population based survey reported that 8.6% of respondents had purchased a homeopathic medicine in the previous

twelve months and 14.6% of respondents had bought an over the counter homeopathic remedy in their lifetime (Thomas et al., 2001).

A survey conducted in 2001 by Thomas & Coleman (2004) estimated that 1.9% of the population of Great Britain had consulted a homeopath in the previous 12 months and that there were 1.13 million visits per year to homeopaths that were paid for out of pocket with an estimated annual out of pocket expenditure of £30.7 million, though some of these visits would have been reimbursed by insurance companies. In addition there was an estimated 180,000 visits that were either free or paid for by charity.

Provision of homeopathy in the UK

The practice of homeopathy in the UK is protected by common law – there is no statutory regulation that directly refers to the practice of homeopathy and no protection of title. Thus anyone, regardless of training and medical qualifications, can call themselves a homeopath. In England the DH policy has been to encourage voluntary self regulation of homeopaths. This is not however the case in many countries where homeopathy can only be practised by medically qualified homeopaths. Homeopaths can be divided into three groups: lay homeopaths, professional homeopaths and homeopathic physicians/ medically qualified homeopaths (ECH Thesaurus).

Lay homeopaths are people who practise homeopathy but who do not belong to a professional register and have not undertaken a recognised training. It is not known how many lay homeopaths there are in the UK.

In the UK there are approximately 3,000 registered professional homeopaths who are neither medically qualified or statutorily regulated. They have undertaken a professional training in homeopathy and belong to professional registers which self-regulate their members with regards to Code of Ethics and Professional Conduct standards. The largest organisation registering homeopaths, the Society of Homeopaths (www.homeopathy-soh.org) has a recognition system for those colleges offering homeopathy practitioner training; courses are four years part time or three years full time. In the UK, five universities currently offer either a BSc in Homeopathy or an e-learning MSc in Homeopathy.

The House of Lords Select Committee on Science & Technology Report on Complementary & Alternative Medicine (2000) recommended the regulation of homeopathy along with the other so called "Group 1" therapies (Acupuncture, Osteopathy, Chiropractic and Herbal medicine) but no steps have been taken to implement regulation of professional homeopaths. A small number (4.5%) of professional homeopaths work within an NHS setting (Partington, 2006) but the majority work from home or in multi-disciplinary Complementary and Alternative Medicine (CAM) clinics charging fees and patients paying for their fees out of pocket. Many health insurers reimburse these fees to patients.

In the UK there are 1,400 homeopaths who are medically qualified as doctors, nurses, vets and podiatrists who have undertaken training with, and are regulated by the Faculty of Homeopathy of whom 400 are GPs. The Faculty of Homeopathy represents and regulates health professionals who provide homeopathy in the NHS. Around 20% of General Practitioners in

Scotland are estimated to have been trained to prescribe homeopathy (Faculty of Homeopathy, 1999).

2.2.6   Provision and use of homeopathy in the NHS

Homeopathy has been available in the NHS since 1948 but the Department of Health does not collect information on the use or provision of homeopathy by homeopaths, or homeopathic medicines, in the NHS. A survey of 1 in 8 GP practices in 2001 (Coleman, 2003) reported that homeopathy was one of the two of the most commonly provided CAM therapies[4].

Patients have access to homeopathy either within the GP practice or by NHS referrals outside the GP practice. Homeopathy provided within the GP practice is either by statutorily registered healthcare practitioners (GP, nurse) trained in homeopathy or by professional homeopaths. Referrals outside the GP practice are to homeopaths working in NHS Trust hospitals, NHS homeopathic hospitals, private consulting rooms, or other GP surgeries. Estimates of the numbers of NHS homeopathy annual visits varies from an estimated 120,000 visits (Thomas et al., 2001) to 200,000

(http://www.trusthomeopathy.org/csArticles/articles/000001/000166.htm accessed 4.10.08) with hospitals providing 55,000 of the 200,000 visits.

There are currently five homeopathic hospitals across Scotland and England (Bristol, London, Tunbridge Wells, Glasgow, Liverpool) which provide a range of conventional and complementary treatments in addition to homeopathy. Normal NHS conditions apply: patients receive services free at the point of care, and hospitals are reimbursed through block contracts with health authorities or extra-contractual referrals. Some professional homeopaths have contracts with general practices and PCTs to provide homeopathic treatment for NHS patients (ABC of Complementary Medicine, 2008).

Two recent publications (Thompson et al., 2008; West Kent, 2007) provide some information on homeopathy currently provided in NHS hospitals. A recent pilot study (Thompson et al., 2008) across all five homeopathic hospitals in the NHS reported the workload of fifty-one medical homeopaths. During a four week period in March 2007 they treated a total of 1,797 patients with the most commonly treated medical complaints being: eczema, chronic fatigue syndrome, menopausal disorder and osteoarthritis and depression.

A consultation document by West Kent Primary Care Trust (West Kent, 2007) reported that West Kent PCT funded 2,800 homeopathy appointments for around 750 people every year at a cost of £192,682 (£250 per person per year). The survey by Thomas et al. (2001) estimated annual NHS expenditure to be £3.3 million.

---

[4] The most commonly provided CAM therapies were: acupuncture, homeopathy, osteopathy, chiropractic, medical herbalism, aromatherapy, reflexology, massage, hypnotherapy & Alexander Technique.

2.3   The current debate: homeopathy in the NHS

Homeopathy has struggled to gain legitimacy in the medical and scientific establishments and is currently a regular subject of debate in the scientific and medical press as well as the popular media. There are active campaigns both for and against homeopathy, particularly its continuing provision in the NHS. Those 'for', cite the popularity of homeopathy and evidence from observational studies of treatment by homeopaths in hospitals and clinics, and from systematic reviews. Those 'against' also cite the evidence from systematic reviews, and highlight the alleged implausibility of homeopathy and question its continuing provision in the NHS. Homeopathy has been described as: *'an effective way of delivering the placebo effect'*, *'quackery'* (Ernst & Pittler, 1998a) and even *'magic'* (Winter, 1991). Popular scientist Professor Richard Dawkins has described homeopathy as *"unproven healing magic"* and *"boldly paddling up the creek of pseudoscience"* (Dawkins, 2007). This section briefly describes several different viewpoints within the debate about homeopathy in the UK: government, the medical and science press and the NHS.

2.3.1   Government

The House of Lords select committee report (2000) stated that:

"*The use of complementary and alternative medicine (CAM) is widespread and increasing across the developed world. This raises significant issues of public health policy such as whether good structures of regulation to protect the public are in place; whether an evidence base has been accumulated and research is being carried out; whether there are adequate information sources on the subject; whether the practitioner's training is adequate and what the prospects are for NHS provision of these treatments. It was the need to consider these issues that prompted this Inquiry.*" (House of Lords, 2000)

Thus the UK government has taken an interest in the regulation, evidence, research, training and possible NHS provision of homeopathy and other forms of complementary and alternative medicine.

2.3.2   The medical & scientific press

The efficacy and cost effectiveness of homeopathy is debated in high profile medical journals (Shang et al., 2005; Horton, 2005; Ross, 2008; Winter, 1991; Kleijnen et al., 1991). On the front page of the BMJ in 2005, (15.10.07) below a picture of homeopathic remedies was the question: *"Complementary and alternative medicine: Is it cost effective?"* In the Lancet, the editor Richard Horton has called for an appraisal of homeopathy by the National Institute for Health and Clinical Excellence (NICE):

"The formulation of guidance based on an appraisal of homeopathy's effects would help to promote the best possible improvement in patient care for the given NHS resources available. NICE guidance would add substantially to the debate about whether and to what extent homeopathy should be available on the NHS" (Horton, 2005).

Horton states that in the absence of such guidance there will "*continue to be inappropriate practice throughout the NHS…... Given the controversy and inevitable uncertainty surrounding*

homeopathic medicine, this subject is a matter of urgent public concern." (Horton, 2005). Thus far the Secretary of State for Health has declined to refer homeopathy to NICE.

Scientific debate has focussed on the implausibility of the principle of potentisation, the second principle of homeopathy. Many have argued that ultra high dilutions do not produce any effect, thus homeopathy trials are seen to be *"a game of chance between two placebos" (Vandenbroucke, 1997).* The author of five systematic reviews of homeopathy and homeopathic remedies commented that the use of: *"highly diluted material that overtly flies in the face of science and has caused homeopathy to be regarded as placebo therapy at best and quackery at worst." (Ernst & Pittler, 1998a).* However, some scientists have readjusted their beliefs in the light of *in vitro* experiments. Professor of Immunology, Madeleine Ennis, who conducted trials of the effect of ultra high dilutions of histamine on basophil activation (Belon et al., 1999, 2004) has been quoted as saying that as a consequence of the results: "*Despite my fundamental reservations against the science of homeopathy, the results compel me to suspend my disbelief and start searching for a rational explanation for our findings."* (Ennis quoted in Seymour, 2001)

2.3.3   National Health Service

The continuing provision of homeopathy in the NHS is frequently challenged e.g. in 2006 Professor Baum and twelve colleagues wrote to the Chief Executives of 472 PCTs in the UK to express their concern about the: *"overt promotion of homeopathy in parts of the NHS (including the NHS Direct website). It is an implausible treatment for which over a dozen systematic reviews have failed to produce convincing evidence of effectiveness"* (*Baum, 2006).* This challenge was repeated by Professor Born and colleagues in May 2007 who wrote to the director of NHS commissioning repeating their concerns about the continued NHS provision of homeopathy in the absence of evidence of efficacy (Born et al., 2007). Some NHS PCTs are reviewing their provision of GP referrals to specialist doctors of homeopathy, for example, West Kent PCT in their consultation document state:

"We're focussing on homeopathy because there is ongoing debate about whether homeopathy provides a cost effective, value for money service and the PCT has a responsibility to ensure that resources are used well" (West Kent PCT Homeopathy Consultation, 2007).

From a societal, governmental and an NHS viewpoint, there is a need for evidence to justify the public and private use of homeopathy and to ask the same questions asked of homeopathy that are asked of other services provided in the NHS. The debate about homeopathy centres around two main questions:

- 'Does homeopathy work?'   - the efficacy question
- 'Should the NHS pay for homeopathy?'   - the cost effectiveness question[5]

---

[5] The cost effectiveness question can be subdivided into further questions such as: Is it safe? Is it acceptable? Will it affect other treatments? Is it effective for condition x in this patient group? What is its effect on quality of life? How much does it cost compared to other treatments with similar effectiveness and safety?

2.4.   The need for evidence

There is debate about the order in which these two questions should be addressed – efficacy or cost effectiveness first? The views of those who argue for and against efficacy to be established before cost effectiveness are now described.

2.4.1   Order of evidence: Efficacy first

The House of Lords Select Committee on Science & Technology report on Complementary & Alternative Medicine (House of Lords, 2000) recommended establishing efficacy before cost effectiveness. The report's summary of recommendations with regards to CAM research recommended the following sequence of research questions: (i) efficacy (ii) safety (iii) cost effectiveness:

"…*three important questions should be addressed in the following order:*
- *(i)   to provide a starting point for possible improvement in CAM treatment, to show whether further inquiry would be useful, and to highlight any areas where is application could inform conventional medicine – does the treatment offer therapeutic benefits greater than placebo*
- *(ii)   to protect patients from hazardous practices – is the treatment safe?*
- *(iii)   to help patients, doctors and healthcare administrators choose whether or not to adopt the treatment – how does it compare, in medical outcome and cost effectiveness, with other forms of treatment? (House of Lords, 2000, p.112)*

Evidence Based Medicine (Sackett et al., 2000a) with systematic reviews of RCTs (predominantly efficacy RCTs) at the top of its hierarchy of evidence implies that healthcare delivery should be shaped by guidelines based on efficacy research. The traditional sequence of research expounded by the MRC (MRC Clinical Trials Unit, 2007) is preclinical research to first establish the theoretical basis for efficacy, then safety trials and efficacy or effectiveness trials, and lastly to comparative effectiveness trials and post marketing surveillance. The British Medical Association (BMA) states that it is supportive of those forms of complementary therapy:

"….for which evidence of claims of efficacy can be demonstrated"

http://www.bma.org.uk/ap.nsf/Content/publicpetitioncam accessed 1.9.08. This view is supported by some CAM researchers who consider it unethical to include non-efficacious treatments in the real world treatment of patients *(*Ernst & Pittler, 2006*).* In summary, the House of Lords select committee, Evidence Based Medicine, MRC, BMA and some CAM researchers all believe that efficacy must be established prior to conducting effectiveness research.

2.4.2   Order of evidence: Effectiveness first

However, the view expounded by Ernst & Pittler (2006) is at odds with the views of many CAM researchers (Fitter & Thomas, 1997; Boon et al, 2006; Fonnebo et al, 2007) who argue that given the existing use of CAM by patients and the limited resources available to national health services, then the need to answer questions of efficacy about CAM treatments is of lower priority than the need to answer questions of cost effectiveness and safety.

The US National Centre for Complementary & Alternative Medicine (NCCAM)[6] model (Table 2.1) suggests five phases for the structure of research in CAM. These phases move from understanding the system as it operates in its real-world setting, documenting potential health benefits (including comparative effectiveness) and then elucidating the mechanisms and efficacy of the intervention (Boon et al., 2006):

Table 2.1   NCCAM model of research

Phase I	Context, paradigms, philosophical understanding and utilization
Phase II	Safety status
Phase III	Comparative effectiveness
Phase IV	Component efficacy
Phase V	Biological mechanisms

UK CAM researchers, Fitter & Thomas (1997) argue similarly that the primacy of the question in the NHS is currently how limited resources should be spent in the best interest of users, which means that the most important question is what is the comparative cost effectiveness of any intervention for a specified population or group?.

Since 2002 the NHS in England and Wales has been legally obliged to provide funding for medicines and treatments recommended by NICE's technology appraisal board. The guidance from NICE is primarily based on clinical and cost effectiveness (www.nice.org.uk). Cost effectiveness is calculated by NICE using cost utility analysis (CUA). CUA estimates the ratio between the cost of a health intervention and the benefit it produces in terms of the number of years lived in full health by the beneficiary. Costs are expressed in pounds and the benefits are usually expressed in quality adjusted life years (QALYs). As of 2005, NICE is believed to have a threshold of £30,000 per QALY (Devlin & Parkin, 2004), thus any health intervention that has an incremental cost of equal to, or less than, £30,000 per additional QALY gained is likely to be accepted as cost effective.

From the NICE and the NHS commissioning viewpoint the most important question is not what is the efficacy of any particular treatment but rather what is the clinical and cost effectiveness of any treatment?

2.4.3   The NHS standpoint: effectiveness first?

The Evidence Based Medicine movement, the House of Lords select committee, the MRC, BMA and some CAM researchers argue that efficacy must be established before attempting to answer questions of clinical and cost effectiveness for homeopathy. However the pharmaceutical research model of establishing efficacy prior to establishing clinical and cost effectiveness is not needed to provide the NHS with the information needed to make decisions regarding provision. This thesis argues that since homeopathy is already in existence in the NHS and other national publicly funded healthcare systems then since there is a desire for cost

---

[6] NCCAM is a US government agency that is dedicated to exploring complementary and alternative healing practices in the context of rigorous science

effectiveness based healthcare decision making in the NHS (heralded by the introduction of NICE) there is a need to produce information as to the cost effectiveness of homeopathy in the NHS regardless of whether or not there is proof for the efficacy for homeopathy.

Box 2.1   Key Criterion I

I   Pragmatic randomised controlled trials

Thus the first criterion from the perspective of the NHS with regards to the type of clinical trial design that can provide the information needed to make decisions about the NHS provision of homeopathy is that trials are pragmatic (effectiveness) trials rather than explanatory (efficacy) trials and that the trials are randomised controlled trials.

2.5   A key problem: the meaning of the term 'homeopathy'

A key problem with the debate is the meaning of the term 'homeopathy'. Having established the need for evidence of the clinical and cost effectiveness of homeopathy, there is a problem which confuses the debate i.e. the multiple meanings of the term 'homeopathy'.

2.5.1   'Homeopathy': multiple meanings

This chapter began with the MeSH description of the term 'homeopathy' which described the 'system of therapeutics' of homeopathy (section 2.2.1). However the term 'homeopathy' has multiple meanings and is often used to refer to one or more of the following:

- Homeopathic medicine (remedies, pills etc).
- Treatment by a homeopath (care by a homeopath, consultation(s) with a homeopath).
- The principles of 'homeopathy' (Principle of similars, Principle of minimum dose etc).

Ambiguity in the use of the term 'homeopathy' is common, with the term sometimes being used to denote two or more different meanings in the same conversation or article. Conclusions drawn from research on one aspect of homeopathy (e.g. homeopathic medicines) are then applied to another meaning of the term (e.g. the therapeutic system of homeopathy). This conflation of meanings is most obvious in systematic reviews of 'homeopathy' (Shang et al., 2005; Kleijnen et al., 1991; Hill & Doyon, 1990) and reviews of systematic reviews of 'homeopathy' (Ernst, 2002; NHS Centre for Reviews & Dissemination, 2002). For example, in a review entitled *'A systematic review of systematic reviews of homeopathy'* (Ernst, 2002) where the primary evidence reviewed was systematic reviews of trials of homeopathic medicines, the author switches between the following terms: *'homeopath' 'homeopathy' 'homeopathic medicines' 'homeopathy's… two principles'*, resulting in confusion as to what the conclusions of the review might possibly refer to.

The lack of differentiation between the various possible uses of the term is further perpetuated by 'homeopathy' being the only MeSH term available for searching the research evidence of homeopathy. If there is to be clarity in the debate then it is of fundamental importance to distinguish between the multiple possible meanings of the term 'homeopathy'. The introduction of additional MeSH terms (e.g. 'homeopathic medicines', 'treatment by a homeopath', and 'the principles of homeopathy') would help facilitate this distinction.

2.5.2 Homeopathic remedy or treatment by a homeopath?

Section 2.4.3 concluded that whether or not there is proof for the efficacy for homeopathy, the evidence required to inform the provision of homeopathy in the NHS is evidence as to the clinical and cost effectiveness of homeopathy. NHS use of homeopathy consists of treatment by someone trained to deliver homeopathy - a homeopath – a practitioner who has been trained in the therapeutic system of homeopathy, prescribing homeopathic remedies according to the principles of homeopathy. GPs refer patients to homeopaths, healthcare commissioners purchase packages of care by homeopaths, patients request treatment from homeopaths, and health insurers pay for treatment with homeopaths. Thus from an NHS decision making standpoint, the primary clinical object of interest with regards to identifying evidence that will inform decision making is 'treatment by a homeopath'.

From an economic angle, the cost of providing 'homeopathy' consists of the cost of the consultation time with the homeopath plus the cost of the homeopathic remedies (50p or less). The cost of a consultation with a NHS homeopath will range from £22[7] (average cost of visit to NHS GP) to £124 (average cost of NHS hospital outpatient attendance). From an NHS decision making standpoint the largest factor in the cost of homeopathic treatment is the cost of the time of the treatment by a homeopath rather than the homeopathic remedies. The recent NHS Quality Improvement Scotland Scoping Report on Homeopathy acknowledged that the *"cost of outpatient treatment is comprised almost entirely of the consultation time for a homeopath"* (NHS QIS, 2006). Thus what is needed is evidence of the clinical and cost effectiveness of 'treatment by homeopaths' rather than clinical and cost effectiveness of homeopathic remedies.

2.5.3 What type of treatment by a homeopath?

There are several different types of homeopathy delivered by homeopaths and this is reflected in several systematic reviews of homeopathy which have analysed trials according to the type of 'homeopathy' used (Kleijnen et al., 1991; Linde et al., 1997; Linde & Melchart, 1998; Ernst, 1999a; NHS Centre for Reviews & Dissemination, 2002). For example the systematic review of placebo controlled trials of homeopathy by Linde et al. (1997) contains a subgroup analysis of four different types of homeopathy: classical, clinical, isopathy and complex; and the NHS Centre for Reviews & Dissemination (2002) review of systematic reviews includes an analysis

---

[7] Information on costs is taken from the Personal Social Services Research Unit (PSSRU) Unit costs of social care 2007 http://www.pssru.ac.uk/uc/uc2007contents.htm accessed 1.9.08

of systematic reviews of trials of individualised homeopathy. The two major types of approaches taken by homeopaths are classical/individualised and formulaic.

Classical/individualised homeopathy

Classical homeopathy (also known as individualised homeopathy) is a treatment approach based on the individualisation of each case, including psychological symptoms and usually uses a single medicine in a single prescription.

"Because homoeopathic prescriptions are based on the recognition of a pattern of symptoms and pathology encompassing the whole state of the patient, and are rarely chosen for one specific syndrome, a single medicine may often be used to treat more than one diagnosis in the same patient, for example asthma and eczema".(Swayne, 1989).

A distinguishing characteristic of the classical/individualised style of homeopathy is that the same medicine is used for a variety of conditions, and the same condition is treated by a variety of medicines: Swayne's (1989) survey of seventy three NHS homeopaths reported that the homeopathic remedy *'Pulsatilla'* was prescribed for problems in seventeen different diagnostic categories, moreover within each diagnostic category a variety of medicines were used e.g. 29 different medicines for eczema, 23 for anxiety, 25 for rheumatoid arthritis. A similarly broad range of homeopathic medicines were reported in a survey of professional homeopaths (Relton et al., 2007).

Formulaic homeopathy

Non classical styles of homeopathy such as isopathy, clinical homeopathy, and complex homeopathy all use categories rather than individualisation and thus can be described as either 'formulaic homeopathy' or sub types of classical homeopathy (Dean, 2004). Classical /individualised homeopathy has emerged since the 1980s as the preferred mode in many parts of the world (Rasky in Dean 2004, p.212) and in the UK is the main type of homeopathy taught and practised by medical and professional homeopaths, especially for the treatment of chronic diseases. Formulaic homeopathy (isopathy, clinical, complex) denotes prescribing methods which are used by homeopaths as and when required. Thus NHS treatment by a homeopath can be modelled or characterised as classical/ individualised homeopathy plus formulaic homeopathy as needed.

2.6   What is 'treatment by a homeopath'

What is involved in treatment by an NHS homeopath? Consultations with a homeopath include an extremely detailed case history. Patients are asked to describe their medical history and current symptoms. Particular attention is paid to the 'modalities' of presenting symptoms – that is, whether they change according to the weather, time of day, season etc. Information is also gathered about mood and behaviour, likes and dislikes, responses to stress, personality and reactions to food. The overall aim of the history taking is to build up a 'symptom picture' of the patient which is then matched with a 'drug picture' as described in the homeopathic *materia medica*. On this basis, one or more homeopathic medicines are prescribed, usually in pill form (ABC of Complementary Medicine, 2008).

The traditional way of understanding or modelling homeopathy is that the homeopathic medicine provides the specific effect and homeopathy trials have studied the effect of homeopathic remedies. However, in the last decade CAM researchers (Long & Mercer, 1999; Vickers, 2000; Fonnebo et al., 2007; Weatherley-Jones et al., 2004b) state that it is irrelevant to focus solely on the specific effects of the homeopathic medicines, and argue that there can be interactions between specific and non specific effects (Weatherley-Jones, 2004b). Further, Fonnebo states that studying the effects of the homeopathic remedy separated from other aspects of homeopathic practice neglects other potentially important components (Fonnebo et al., 2007). Vickers (2000) describes an attempt to design a trial whose purpose was to separate out the 'specific and non specific effects of homeopathy', the first time that a trial of homeopathy has acknowledged the importance of researching factors other than the specific effects of the homeopathic medicine.

2.6.1   Treatment by a homeopath: remedy +?

A recent RCT of adjunctive treatment by a homeopath (Relton, in press) describes treatment by a homeopath as a *"series of in depth interviews with a strong focus on the patient's subjective experience, plus individually tailored homeopathic medicines".* There is a growing literature that examines the complexity of treatment by a homeopath which reveals elements in treatment by a homeopath other than the homeopathic remedy. For example, Van Hootegem (2007) in relating the case of a 23 year old woman with chronic fatigue syndrome who was cured with a course of homeopathic treatment states: *"the action of the homeopathic medicine was intimately woven with the relationship I had with her as a therapist. It is impossible to separate these two influences".* And Kaplan, a highly experienced medically qualified homeopath states: *"It took me nearly two decades to realise something obvious about classical homeopathy – the conversations we have with our patients are the most important part of the whole process" (Kaplan, 2001).* Homeopathic remedies are an intrinsic part of 'treatment by a homeopath' but the consultation with the homeopath involves other elements e.g. a therapeutic relationship.

2.6.2   A complex intervention

The Medical Research Council (MRC) (2000) conceptual *'Framework for development and evaluation of RCTs for complex interventions'* has been suggested as a helpful approach to understanding *'the riddle of homeopathy'* (Thompson, 2006; Thompson & Thompson 2006). The biomedical model of evaluating disease has traditionally emphasized the evaluation of single component interventions; however, researchers recognise the need for a new conceptual framework for assessing complex healthcare systems (Medical Research Council, 2000; Verhoef et al., 2004; Fonnebo et al., 2007; National Center for Complementary and Alternative Medicine, 2005). Thompson (2006) argues that approaching homeopathy as a complex intervention is justified as the homeopathic approach contains a number of components which may act both independently and interdependently, as consultations with a homeopath….

"… involve the patient in an unusually detailed exposition of their complaints, an attentive practitioner and a process of matching between the patient's predicament and what is known of a wide range of homeopathic medicines. Thus even on prima facie grounds there are a number of potential factors at play" (Thompson, 2006)

This thesis argues that 'treatment by a homeopath' is best understood not just as the prescription of a homeopathic remedy but as a complex intervention with a number of components which may act both independently and interdependently[8].

2.7   Modelling treatment by a homeopath

The MRC Framework document (2000) suggests that there should be a modelling phase in the process of development/evaluation of all complex interventions in order to "*develop an understanding of your intervention and its possible effects" (MRC, 2000)*. Modelling consists of delineating an intervention's components, how they inter-relate and how the active components of a complex package may relate to outcomes. This section examines how treatment by a homeopath has been modelled through an examination of the literature with reference to the writings of Kaplan (2001), Konitzer (2003), Scott (1998), Weatherley-Jones (2004b), Thompson & Thompson (2006), and the results of qualitative research conducted by Thompson (2006), Chatwin (2002) and Eyles (2008).

2.7.1   The therapeutic relationship
Sociologists (Chatwin & Collins, 2002) have studied interaction in the homeopathic consultation using conversational analysis. Conversational analysis (CA) is largely concerned with the analysis of the verbal communicative practices that people routinely use when they interact with one another and has been used as a method for research into interactions between patients

---

[8] This argument can be extended to any healthcare intervention (including the prescription of pharmaceutical interventions) where there is interaction between humans (and thus the possibility of a therapeutic relationship).

and healthcare professionals (Drew et al., 2001). Through the analysis of a large number of homeopathic consultations, Chatwin & Collins found that:

- there was a high degree of mutuality between patient and practitioner (e.g. mutual laughter)
- the intrinsic form of the consultation enabled the practitioner to be more subtle in the maintenance of their role as 'expert'
- the homeopath actively incorporated the patient's own medical reasoning process, treating this reasoning as valid and relevant
- there was active involvement in deductive reasoning activities

Weatherley-Jones et al. (2004b) also highlighted the therapeutic nature of the relationship between the patient and homeopath in discussing what can and cannot be deduced from placebo controlled trials of complementary and alternative medicine: *"… in homeopathic treatment of chronic physical problems, the therapeutic relationship develops over a period of time and there are a series of detailed consultations involving comprehensive assessment of emotional as well as physical states"* (Weatherley-Jones et al., 2004b).

2.7.2 The homeopathic conversation

The disciplines of psychotherapy and counselling have always recognised the therapeutic relationship to be a vital factor in the prognosis for the patient; however, not until recently have homeopaths & homeopathy researchers focused on the therapeutic relationship between patient and homeopath e.g. Kaplan (2001) stresses the importance of rapport and the need for *'authentic conversations'* with patients. Scott (1998) writes about how many alternative medicines (including homeopathy) help patients address their illness or disability through a process of *'narrative reconstruction'*, a process by which they account for their illness through a reorganisation of their own biographies. Konitzer et al. (2003) uses a metaphorical, narrative model to explain the outcome of a homeopathic encounter involving the patient, practitioner and the homeopathic medicine.

2.7.3 Other ingredients

Homeopath researchers have used qualitative research methods in an attempt to understand the homeopathic approach. Thompson (2006) used patient based research and identified six putative active ingredients which may account for the effectiveness of homeopathic care: patient's openness to the mind body connection, consultational empathy, in depth enquiry into bodily complaints, disclosure, the remedy matching process, and homeopathic remedies. Eyles (2008) focussed on practitioner perspectives of the homeopathic approach and proposed a model to describe what happens in the consultation which includes actively connecting, exploring the journey together, finding the level, responding therapeutically, and understanding self.

2.7.3 Modelling treatment by a homeopath in trials

The majority of 'homeopathy' trials compare homeopathic remedies to placebo in order to establish the efficacy of the intervention. Placebo trials involve dummy treatments and trial participants are told that they may receive a dummy treatment. Sceptics argue that all homeopathic remedies are placebo (Ernst & Pittler, 1998a) and others argue that there is a 'placebo effect of the therapeutic relationship' (Wall & Wheeler, 1996). Yet regardless of whether homeopathic remedies are or are not placebos, homeopaths (like all healthcare practitioners) do not inform their patients that they may receive a placebo (dummy) treatment as this information will obviously sabotage the therapeutic relationship between patient and practitioner. Kaplan (2001) and Thompson (2006) talk about the homeopathic consultation and the therapeutic relationship between patient and homeopath using terms such as authenticity, rapport, focus, empathy. Their work emphasises that the therapeutic relationship is necessary for the 'proper functioning' of the healthcare intervention of treatment by a homeopath. Yet providing the patient with information that they might receive a placebo treatment (as is the case in all efficacy trials) will sabotage the therapeutic relationship. The MRC Framework document states that complex interventions in healthcare: *"… comprise a number of separate elements which seem essential to the proper functioning of the intervention….". (MRC, 2000).* If the complexity of treatment by a homeopath is to function properly in a clinical trial then the overt use of placebos in the trial design is not possible. Thus from the perspective of the intervention (homeopaths and homeopathy in the NHS) the second key criterion for clinical trial design is that it allows the complexity and proper functioning of the intervention (Box 2.2).

Box 2.2   Key Criterion II

II	Allows the complexity and proper functioning of the intervention

2.7.5   Summary

'Homeopathy' in the context of the pursuit of evidence as to the clinical and cost effectiveness of homeopathy is best understood as 'treatment by a homeopath' and NHS homeopaths use the individualised style of homeopathy. There have been several attempts to model 'treatment by a homeopath' all of which highlighted the consultation and the relationship between the patient and the practitioner as essential ingredients in the complexity of 'treatment by a homeopath'. This section also highlighted the importance of the 'proper functioning of the intervention' when it is being evaluated, drawing the conclusion that the overt use of placebos does not allow the proper functioning of treatment by a homeopath. Thus evidence that could inform NHS decision making regarding the provision of homeopathy or NICE guidance needs to meet key criteria I and II for appropriate trial design:

Box 2.3   Key criteria I & II

I	Pragmatic randomised controlled trials
II	Allows the complexity and proper functioning of the intervention

This chapter has established that the first key criterion for evidence from the NHS perspective on the intervention is that the evidence is derived from pragmatic RCTs of clinical and cost effectiveness of treatment. For the intervention 'homeopathy' (in the NHS) that translates into evidence as to the clinical and cost effectiveness of 'treatment by a homeopath' using predominantly the classical/individualised type of homeopathy. The second key criterion for appropriate pragmatic clinical trial design for any intervention is that the design allows the complexity and proper functioning of the intervention. For the intervention 'treatment by a homeopath' this means that there is no role for the overt use of placebos in the pragmatic RCT design. The aim of section 2.8 is to search for this type of evidence.

2.8   Searching for the evidence: a review of systematic reviews of 'homeopathy'

It has been claimed that with regards to the provision of homeopathy in the NHS: *"There is now a sufficient evidence base on which to decide such guidance (from NICE)" (Horton, 2005).* Indeed hundreds of trials and many systematic reviews of these trials have been published. This section considers the evidence from these systematic reviews.

2.8.1   Search strategy for identifying systematic reviews
The following major electronic bibliographic databases were searched: Medline (via Ovid) 1950 to July 2007, AMED (Allied & Complementary Medicine) 1985 to July 2007, Embase 1980 to 2007 week 31, the Cochrane library and Cinahl 1982 – 2007. In addition the NHS CAM specialist library - http://www.library.nhs.uk/cam/ and three homeopathy specific databases were searched:

- Hominform. http://hominform.soutron.com/homqbe1.asp
- European Committee for Homeopathy (ECH): http://www.homeopathyeurope.org/
- European Committee for Classical Homeopathy: http://www.homeopathy-ecch.org/

The term 'treatment by a homeopath' and it's synonyms alone were too narrow to use as search terms, so in order to ensure that all reviews of treatment by a homeopath were identified, a broad approach was adopted which used the following search terms: homeopath$, homoeopath$, AND systematic review OR meta-analysis, excluding non English articles.

Inclusion criteria: all types of systematic reviews of controlled trials of homeopathy conducted with human patients including reviews of systematic reviews, comparative systematic reviews and overviews of systematic reviews of clinical trials of homeopathy.

Exclusion criteria: clinical trials, reviews of non clinical investigations, duplicates, non English language reviews, CAM general systematic reviews, reviews of provings/human pathogenetic trials (HPTs) trials/homeopathic aggravations, comments and opinion pieces and protocols for systematic reviews, non homeopathy systematic reviews, systematic reviews not of clinical trials, and systematic reviews of animal studies.

2.8.2   Description of systematic reviews identified

The search strategy identified a total of 25 systematic reviews. Analysis of the systematic reviews was hampered by the lack of clarity as to whether 'homeopathy' referred to: treatment by homeopath, homeopathic remedies, the system of homeopathy, or the principles of homeopathy. 5/25 systematic reviews were clearly systematic reviews of homeopathic remedies (Ernst & Pittler, 1998a; Ernst & Barnes, 1998b; Long & Ernst, 2001; Wiesenauer & Ludtke, 2000; Vickers & Smith, 2006) and were clear and consistent throughout that they were reviews of homeopathic remedies rather than any other aspect of 'homeopathy'. However 20/25 of the systematic reviews used the following terms in their title: 'homeopathy', 'homeopathic treatment', 'homeopathic therapy' or 'homeopathic prophylaxis'; and within these reviews the term 'homeopathy' often had undefined multiple meanings. As there was heterogeneity in focus in these reviews, five categories of review were created and the characteristics of each reported below and in Tables 2.2 and 2.3:

- Systematic reviews of all clinical trials (3/25)
- Systematic reviews of placebo controlled trials (2/25)
- Systematic reviews of specific condition/remedies/patients groups (17/25)
- Systematic reviews of individualised homeopathy trials (2/25)
- Comparative systematic reviews of homeopathy (1/25)

A. Systematic reviews of all clinical trials

Three systematic reviews of all trials were identified (Table 2.2) (Hill & Doyon, 1990; Kleijnen et al., 1991; Dean, 2004[9]). Hill & Doyon's review of 40 RCTs concluded that the results did not provide acceptable evidence of the effectiveness of 'homeopathic treatments', whereas Kleijnen et al.'s much larger review included 68 RCTs and 39 controlled clinical trials and concluded that the results were *"positive but insufficient to draw definitive conclusions due to low methodological quality of trials and the unknown role of publication bias".* Dean's larger review of 52 controlled clinical trials and 153 RCTs reported significant results or strong trends for significance for the majority of trials of homeopathy.

B. Systematic reviews of placebo controlled trials

---

[9] Dean's review (2004) was peer reviewed for his PhD thesis rather than peer reviewed for publication.

The two systematic reviews of placebo only controlled trials (Table 2.2) (Cucherat et al., 2000; Linde et al., 1997) reported cautious yet positive conclusions as to the efficacy of 'homeopathic treatments/ homeopathy'.

C. Systematic reviews of specific conditions/remedies/patient groups

Seventeen systematic reviews of specific conditions/remedies/patient groups have been published since 1998 (Table 2.3). Three systematic reviews reviewed the effects of specific homeopathic remedies (Ernst & Pittler, 1998a; Vickers & Smith, 2006; Wiesenauer & Lütdke, 2000) while the majority (13/17) have been systematic reviews of specific conditions. Results were reported as positive or encouraging by five systematic reviews: post operative ileus (Barnes et al., 1997), osteoarthritis (Long & Ernst, 2001), preventing and treating influenza like syndromes (Vickers & Smith, 2006), pollinosis (Wiesenauer & Lütdke, 2000) and cancer treatment (Milazzo et al., 2006). Results were reported as no better than placebo by two systematic reviews: headaches and migraines (Ernst, 1999b) and Arnica (Ernst & Pittler, 1998a). The remaining ten systematic reviews reported that their results were inconclusive either because of insufficient evidence or evidence that was unconvincing or contradictory.

D. Systematic reviews of individualised homeopathy

There were two reviews of individualised homeopathy (Table 2.3): (Ernst 1999a, Linde & Melchart, 1998). Both reported methodological shortcomings and inconsistencies but drew different conclusions as to whether they demonstrated the efficacy of homeopathic remedies (Linde & Melchart, 1998) or whether the efficacy of homeopathic remedies was *'not known'* (Ernst, 1999a). Despite focussing on individualised homeopathy neither review discussed treatment by a homeopath.

E. Comparative systematic reviews

The only comparative systematic review (Table 2.3) that compared the efficacy of 'homeopathy' with that of allopathy (Shang et al., 2005) concluded from its meta-analysis that there was weak evidence for a specific effect of homeopathic remedies. However, Lütdke & Rutten (2008) have shown that the meta-analysis results change sensitively to the chosen threshold defining large sample sizes and conclude that the results and conclusions are less definite than they had been presented. Others have suggested that the results are *ad hoc* rationalisations and that the publication of Shang et al., (2005) was a result of a *"breakdown of peer review and standards"* (Frass, 2005).

Table 2.2   **Systematic reviews of all trials, placebo controlled trials and individualised homeopathy trials**

Type	Author/ year	Title	Conclusion	CCTs*	RCTs**
Systematic reviews of all clinical trials	**Kleijnen et al. 1991**	Trials of homeopathy	*"evidence of clinical trials is positive but not sufficient to draw definitive conclusion because most trials are of low methodological quality and because of the unknown role of publication bias"*	39	68
	Hill & Doyon 1990	Randomised trials of homeopathy	*"results do not provide acceptable evidence that homoeopathic treatments are effective"*	0	40
	Dean 2004	Trials of homeopathy 1940 - 1995	*"the majority of trials reported positive effects, either significant or strong trends, regardless of the type of control or homeopathy that was trialled"*	52	153
Systematic reviews of Classical/Individualised homeopathy	**Ernst 1999a**	Classical homeopathy vs conventional treatments	*"It is concluded that at present the relative efficacy of homeopathic remedies is not known"*	3	3
	Linde & Melchart 1998	RCTs of individualised homeopathy	*"the results of the available randomized trials suggest that individualised homeopathy has an effect over placebo."*	8	24
Systematic review of placebo controlled trials	**Linde et al. 1997**	Are the clinical effects of homeopathy placebo effects? A meta analysis of placebo controlled trials	*"the results of our meta-analysis are not compatible with the hypothesis that the clinical effects of homoeopathy are completely due to placebo. However, we found insufficient evidence from these studies that homoeopathy is clearly efficacious for any single clinical condition"*	0	89
	Cucherat et al. 2000	Evidence for clinical efficacy of Homeopathy	*"there is some evidence that homeopathic treatments are more effective than placebo; however, the strength of this evidence is low because of the low methodological quality of the trials"*	0	17
Comparative systematic review of allopathic and homeopathy placebo RCTs	**Shang et al. 2005**	Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of allopathy vs homeopathy	random or quasi random assignment *"there was weak evidence for a specific effect of homeopathic remedies, but strong evidence for specific effects of conventional interventions. This finding is compatible with the notion that the clinical effects of homeopathy are placebo effects".*	0	110 vs 110

Author/year	Title	Purpose	CCT*	RCT**	Conclusion
Altunc et al. 2007	Homeopathy for childhood & adolescence ailments	To assess the evidence of any type of therapeutic or preventative intervention testing homeopathy for childhood and adolescence ailments	0	16	*"…not convincing enough for recommendations in any condition"*
Barnes et al. 1997	Homeopathy for post operative ileus: a meta-analysis	To determine whether homeopathic treatment has any greater effect than placebo administration on the restoration of intestinal peristalsis in patients after abdominal or gynaecologic surgery	0	6	*"There is evidence that homeopathic treatment can reduce the duration of ileus after abdominal or gynaecologic surgery"*
Coulter et al. 2006	Attention-deficit hyperactivity disorder/ hyper-kinetic disorder	To evaluate the evidence for the efficacy and safety of homoeopathy for treating ADHD or HKD	0	4	*"The efficacy of homoeopathy for ADHD/HKD is uncertain"*
Ernst & Pittler 1998a	Are homeopathic remedies effective for delayed onset muscle soreness?	To determine whether homeopathic remedies are more effective than placebo in reducing the signs and symptoms of DOMS	5	3	*"Evidence does not support the hypothesis that homeopathic remedies… are more efficacious than placebo"*
Ernst & Barnes 1998b	Efficacy of homeopathic arnica	To systematically review the clinical efficacy of homeopathic arnica	4	4	*"The claim that homeopathic arnica is efficacious beyond a placebo effect is not supported by rigorous clinical trials"*
Ernst 1999b	Homeopathic prophylaxis of headaches & migraines	To evaluate the clinical trials, testing the efficacy of homeopathy for the prophylaxis of migraine and headaches	0	4	*"Trial data.. do not suggest that homeopathy is effective in the prophylaxis of migraine or headache beyond a placebo effect"*
Jonas et al. 2000†	Homeopathy and rheumatic disease				
Long & Ernst 2001	Homeopathic remedies for the treatment of osteoarthritis	To assess all RCTs of homeopathy in the treatment of patients with OA	0	4	*"There appeared to be a positive trend towards the effectiveness of combination homeopathic preparations … the small number of trials preclude firm conclusions"*
McCarney et al. 2003	Homeopathy for dementia	To evaluate the effectiveness and safety profile of homeopathically prepared medications used in treating dementia	0	1	*"There were no studies that fulfilled the criteria for inclusion"*

McCarn ey et al. 2004	Homeopathy for chronic asthma	The objective of this review was to assess the effects of homeopathy in people with chronic stable asthma.	0	6	*"There is not enough evidence to reliably assess the possible role of homeopathy in asthma"*
Milazzo et al. 2006	Efficacy of homeopathic therapy in cancer treatment	To evaluate the effectiveness of any type of homeopathic therapy in the treatment of patients with cancer	1	4	*"Although the evidence was encouraging, there was insufficient evidence to support the use of homeopathy"*
Owen & Green 2004	Homeopathic treatment of headaches	To review trials relating to the homeopathic treatment of tension type, cervicogenic and migraine headache	0	4	*"Insufficient evidence to support or refute the use of homeopathy"*
Pilkingt on et al. 2005	Homeopathy for depression	To evaluate the effectiveness, including safety and patient satisfaction of homeopathy for the treatment of depression	0	3	*"Evidence for the effectiveness of homeopathy in depression is limited because of a lack of high-quality trials"*
Pilkingt on et al. 2006	Homeopathy for anxiety and anxiety disorders	To conduct a systematic review of the clinical research evidence on homeopathy in the treatment of anxiety and anxiety disorders	?	8	*"RCTs report contradictory results, are underpowered or provide insufficient details of methodology. (Several observational studies reported positive results)"*
Smith 2004	Homeopathy for induction of labour	To determine the effects of homoeopathy for third trimester cervical ripening or induction of labour	0	2	*"There is insufficient evidence to recommend the use of homoeopathy as a method of induction"*
Vickers & Smith 2006	Homeopathic oscillicoccinum for preventing and treating influenza like syndromes	To determine whether homeopathic Oscillococcinum or similar medicines are more effective than placebo in the preventions and treatment of influenza and influenza like syndromes	0	7	*"Though promising the data were not strong enough to make a general recommendation to use Oscillococcinum"*
Wiesen auer 2000	A meta-analysis of the homeopathic treatment of pollinosis with Galphimia glauca	To assess the efficacy of homeopathically prepared Galphimia glauca compared with placebo in the treatment of pollinosis	4	7	*"Significant superiority of Galphimia glauca over placebo is demonstrated"*

2.8.3   Summary

No systematic reviews of pragmatic RCTs or the clinical effectiveness of treatment by a homeopath were identified; instead systematic reviews focussed either on the efficacy question (placebo trials) or combined all RCTs regardless of comparator (placebo or other treatments).

2.9   Searching for the evidence: treatment by a homeopath

2.9.1   The conditions for NHS evidence of 'homeopathy'

Despite the lack of relevant systematic reviews, it is possible that there might be pragmatic RCTs of treatment by a homeopath? This section attempts to identify whether, within the homeopathy systematic reviews identified in the above review, there are trials which fulfil the conditions for evidence that can inform NHS decision making regarding the clinical and cost effectiveness of homeopathy:

a) fulfil the two key criteria for appropriate clinical trial design from the perspective of an intervention: pragmatic randomised controlled trial (I) which allows the complexity & proper functioning of the intervention (II)

b) meet the requirements for evidence of clinical and cost effectiveness for homeopathy from an NHS standpoint: treatment by a homeopath (principally using individualised homeopathy) that do not include the overt use of placebos.

2.9.2   A pragmatic RCT of individualised homeopathy

It is possible to identify a significant number of trials which used individualised homeopathy (and thus involved one or more consultations with a homeopath using the individualised type of homeopathy) as there are two systematic reviews of individualised homeopathy (Linde & Melchart, 1998; Ernst, 1999a). Ernst's 1999 systematic review 'Classical Homeopathy versus conventional treatments' reviews three randomised trials, two of which use placebo in the control arm, thus there is one RCT of individualised homeopathy (Owen, 1990). Linde & Melchart (1998) review 32 RCTs of which 31 use placebo in the design which leaves just one non placebo RCT of individualised homeopathy (Lecoyte, 1993) which is a duplicate publication of the RCT by Owen (1990).

Thus there is one RCT (Owen, 1990) which fulfils conditions a & b – the evidence needed to inform decision making regarding the NHS provision of homeopathy. This was a parallel group randomised controlled trial comparing treatment by a homeopath to orthodox treatment as usual for Irritable Bowel Syndrome. The homeopathy was individualised/classical homeopathy and treatment as usual/conventional treatment was dicyclomine hydrochloride + fecal bulking agents + advice sheets. The 23 female patients were followed up for 12 weeks. Clinical outcomes were reduction in participant selected worst symptoms using a VAS. There was no difference between the groups in terms of clinical outcomes.

2.9.3   Comparison with other reviews of systematic reviews

During the search for systematic reviews one Health Technology Assessment (Bornhoft et al., 2006) was identified as well as one NHS Centre for Reviews and Dissemination bulletin (NHS CRD, 2002), one critical overview of homeopathy (Jonas et al., 2003), one systematic review (Linde et al., 2001) and one systematic review of systematic reviews (Ernst, 2002). All reviews were published between 2001 and 2006, four in the UK and one in Germany and reviewed between 14 and 22 systematic reviews. The two most influential reviews of systematic reviews of homeopathy (CRD, 2002; Ernst, 2002) both concluded that there was insufficient evidence to make positive recommendations for the use of homeopathy for specific conditions. But, two other reviews (Linde et al, 2001; Jonas et al., 2003) found promising evidence for homeopathic treatment for some conditions: influenza, pollinosis, allergies, post operative ileus, childhood diarrhoea. One HTA review (Bornhoft 2006) concluded that the 22 systematic reviews gave 'sufficient evidence for effectiveness of homeopathy'.

The lack of clarity in terms presents difficulties in attempting to understand the conclusions of these reviews of systematic reviews. For example, Ernst's 'Systematic review of systematic reviews' (Ernst, 2002) uses the following terms interchangeably: 'homeopath' 'homeopathy' 'homeopathic medicines' 'homeopathy… two principles' in relation to the evidence.

The most influential review of systematic reviews for decision makers (NHS CRD, 2002), was conducted by the University of York Centre for Reviews and Dissemination[10] and as published describes itself as a: '*Bulletin on the effectiveness of health service interventions for decision makers. This bulletin summarises the research evidence on the effectiveness of homeopathy*'. The authors, however, do not discriminate between treatment by a homeopath, homeopathic remedies and the system of homeopathy. The conclusions drawn by this systematic review are thus difficult to apply to the questions that decision makers need answers to.

2.9.4   Searching for the evidence: Non RCT evidence of treatment by a homeopath

There is a considerable amount of non RCT clinical 'homeopathy' evidence which reports the outcomes of treatment by homeopaths, rather than homeopathic remedies. This non RCT evidence is in the form of observational studies of groups or series of patients with validated quantitative outcome measures data from before and after treatment, and single case studies written in narrative style. The amount of this type of evidence published is considerable: 30 + observational studies/case series and 10,000+ single case studies[11] [12]. Observational studies report the outcomes of treatment by homeopaths in everyday clinical settings and all appear to report improved outcomes for the majority of their study participants. An observational study

---

[10] The CRD is also currently conducting a number of Cochrane reviews (acute respiratory tract infections in children, preventing recurrent acute respiratory tract infections in children, adverse effects of cancer management and osteoarthritis).

[11] A search of the online Medline database identified 507 single case reports/case series are however, the majority of single case studies are published in the 'grey' (non online) literature.

[12] Personal communication with archivist of the therapeutic system of homeopathy Francis Treuherz (April 2007)

(Spence et al., 2005) reported outcomes of treatment by a homeopath in the NHS with data on 6,544 patients. Comparative studies comparing homeopathic treatment to a conventional treatment report better outcomes for the homeopathic patients (Riley et al., 2001; Friese et al., 1997; Witt 2005a). However, the research methods mean that the evidence can be vulnerable to substantial biases including regression to the mean, patient selection bias and outcome measurement bias. Individual case studies are often vulnerable to forms of additional bias: observer bias, recall bias, and analysis assessment bias. Any bias may exaggerate or deflate the true effect of the treatment.

2.10   Conclusion

The purpose of chapter 2 was to examine the question: *"What type of clinical trial design can provide the information needed to make decisions about the provision of homeopathy in a publicly funded healthcare system?"* from the perspective of homeopathy in the NHS. This chapter described the therapeutic system of homeopathy and other multiple meanings of the term 'homeopathy': homeopathic remedies, the principles of homeopathy, treatment by a homeopath. It established that treatment by a homeopath is not the same as homeopathic remedies or the therapeutic system of homeopathy, but is a distinct complex intervention which includes a variety of ingredients (e.g. patient's openness to the mind body connection, consultational empathy, in depth enquiry into bodily complaints, disclosure, the remedy matching process, and homeopathic remedies) any or all of which may account for the effectiveness of treatment by a homeopath.

Homeopathy has been provided by the NHS for 60 years yet there is debate regarding its continuing provision. This debate focuses on the efficacy of homeopathic remedies and the cost effectiveness of the provision of homeopathy. However homeopathy in the NHS is provided by homeopaths and although they use homeopathic remedies the bulk of the cost of homeopathy is the cost of treatment by the homeopath; thus the central questions from the NHS perspective relate to questions as to the clinical and cost effectiveness of treatment by a homeopath rather than the efficacy of homeopathic remedies.

Two key criteria for appropriate clinical trial design from the perspective of the intervention (homeopathy in the NHS) were identified: pragmatic randomised controlled trials (I) which allow the complexity and proper functioning of the intervention (II).

A review of systematic reviews was conducted in order to identify evidence that could be used to inform decision making regarding the NHS provision of homeopathy. Of the 150+ RCTs only one pragmatic RCT of treatment by a homeopath was identified (Owen, 1990) which reported that treatment by a homeopath was equivalent to usual care.

The search for evidence of pragmatic RCTs of treatment by a homeopath has highlighted several issues and several recommendations are made.

Recommendations

- There is a need to improve future reporting of 'Homeopathy' trials through the inclusion of information on consultations, practitioners, theoretical models, case analysis strategies etc. The implementation of the recent 'RedHot' supplement to CONSORT guidelines (Dean et al., 2007) will help this.

- In order to promote clarity in the reporting, design and interpretation of 'homeopathy' research, the term 'Homeopathy' should be solely used to refer to the 'therapeutic system of homeopathy'.

- In order to promote clarity in the reporting, design and interpretation of 'homeopathy' research the MeSH term 'homeopathy' has additional subheadings to help differentiate various aspects of the therapeutic system of 'homeopathy': 'homeopathic medicines',' treatment by a homeopath', 'the principles of homeopathy' etc and that these are used in the reporting of research e.g. 'RCT of the efficacy of homeopathic medicine for …' or 'An observational study of treatment by a homeopath'.

- To ensure clarity in debate about 'homeopathy' and the 'homeopathy' evidence base, the exact aspect of 'homeopathy' being discussed is made explicit and the evidence referred to matches the evidence required by the nature of the question being debated.

Chapter 3

The condition: menopausal hot flushes

3.1   Introduction

Chapter 2 examined appropriate clinical trial design from the perspective of a particular
intervention, 'homeopathy', and identified two key criteria for clinical trial design which can
provide the information needed to inform decision making about the NHS provision of
homeopathy. Chapter 3 now turns to examining appropriate clinical trial design from the
perspective of the condition, and as it is hard to think about this question in the abstract, an
example condition has been chosen: 'menopausal hot flushes'. Part of the rationale for
choosing this particular condition is that it is one of the most commonly treated conditions in
NHS homeopathic hospitals (Thompson et al, 2008).

3.1.1 Aim and objectives

The aim of this chapter is to identify key criteria for appropriate clinical trial design from the
perspective of the condition - menopausal hot flushes. The objectives of this chapter are to:

- Describe the epidemiology and physiology of hot flushes
- Describe the most commonly prescribed treatment for hot flushes (HRT)
- Report the methods and results of research on HRT for menopausal problems
- From the HRT research, draw out the methodological implications for future research
- Report what is known about non HRT treatments for hot flushes, including the results of
  a systematic review of 'homeopathy' for menopausal symptoms
- Discuss the future direction of research into menopausal hot flush treatments

3.2. The condition: Menopausal hot flushes

3.2.1 The menopause

The word 'Menopause' is derived from the Greek *menos* (month) and *pausos* (an ending) and strictly means - the final menses, A woman's status as having 'gone through the menopause' can only be defined retrospectively one year later when no more menstrual periods have occurred. The term 'menopause' is more commonly used to mean the time before and after the final menses and is divided into three sections: pre, peri and post menopause (World Health Organisation, 1996). 'Pre menopause' refers to the whole of the reproductive period prior to the menopause. 'Peri menopause' begins with the first clinical, biological and endocrinological features of the approaching menopause –vasomotor symptoms and menstrual irregularity, and ends 12 months after the last menstrual period. 'Post menopause' refers to any time after the final menstrual period.

The median age of the naturally occurring menopause is around 49 to 51 years of age (Kronenburg, 1990) with the majority of women going through the menopause between 45 and 55 years. In 2000 there were 3.9 million women in the UK in this age group (http://www.statistics.gov.uk/cci/nugget.asp?id=6 accessed 26.8.08). However some women experience a premature or early menopause (before the age of 45), and the menopause can be brought on artificially either by oopherectomy (surgical menopause) or as a result of radiotherapy and chemotherapy treatment for cancer.

Although there are overall changes in hormone levels during the menopausal transition years, these hormone levels fluctuate on a daily basis and vary so much between women that there are no reliable biological markers for the menopause. Many clinicians, however, in daily practice consider FSH (Follicle Stimulating Hormone) levels greater than 30 IU/L (international units per litre) to be in the post menopausal range but use other additional signs and symptoms to determine a woman's menopausal status.

The biomedical perspective of the menopause and the identification of the menopause as a disease of oestrogen[13] deficiency gained ascendancy with the publication of the book 'Feminine Forever' (Wilson, 1966). Over the following years, guidelines on management of the menopause began to link a wide range of symptoms and chronic diseases to changes in hormone levels e.g. osteoporosis, cardiovascular disease, coronary heart disease (CHD), and stroke (BMS, 2002). Oestrogen replacement (HRT) came to be seen as not only effective in relieving the vasomotor and psychological symptoms of the menopause, but also as having long term benefits in terms of preventing the long term 'consequences' of the menopause - osteoporosis, CHD and cardiovascular disease.

---

[13] Oestrogen and estrogen are different spellings of the same hormone

3.2.2   Menopausal hot flushes

Vasomotor symptoms (hot flushes, hot sweats, night sweats and chills), sleep disturbances, mood swings and cognitive deficits are most commonly reported during the menopausal transition (Utian, 2005). Hot flushes are subjectively defined as *"recurrent transient periods of flushing, sweating and a sensation of heat, often accompanied by palpitations and a feeling of anxiety and sometimes followed by chills"* (Kronenburg, 1990). They can occur at any time of the day and at night when normal sleep patterns may be disturbed (when they are commonly referred to as night sweats). Night sweats sometimes result in chronically disturbed sleep, which can in turn lead to insomnia, irritability and difficulties with short term memory and concentration. Approximately 70 – 80% of women in Western cultures experience vasomotor symptoms such as hot flushes and night sweats. Symptoms such as depression, anxiety, insomnia, poor concentration and a reduced libido are associated with hot flushes.

3.2.3   Hot flush definitions

'Hot flushes', 'hot sweats' and 'night sweats' are all different ways of describing menopause related vasomotor symptoms. In this thesis the term 'hot flush' is used to collectively refer to all menopause associated vasomotor symptoms. Hot flushes are primarily a phenomenon of menopausal women but can be experienced by premenopausal women, women with Pre Menstrual Syndrome (PMS), during pregnancy or immediately after childbirth. Hot flushes can also be caused by systemic disease, neurological disorders, alcohol, drugs and food additives (Stearns et al., 2002). This thesis focusses on menopause related hot flushes.

3.2.4   Epidemiology of menopausal hot flushes

For most women the experience of hot flushes lasts between 6 months to 2 years (Kronenburg et al., 1994; Utian, 2005). However, a third of women have hot flushes for up to five years and 10% have hot flushes for more than 10 years (Feldman et al., 1985). Hot flushes are most frequently reported during the first 2 years after the last period (Utian, 2005). Hot flushes vary in duration, frequency and intensity so quantitative assessment can be difficult. Objective measures of assessment are invasive so the majority of studies use subjective measures of hot flushes with women describing both the intensity and the frequency of their hot flushes.

3.2.5   Physiology of hot flushes

The physiology of hot flushes is not clearly understood, but they are thought to arise as an alteration of the central nervous system thermoregulatory set-point located in the anterior portion of the hypothalamus as a result of cross talk between gonadal hormones especially oestrogen. How oestrogen affects this balance is unknown (Stearns et al., 2002).

3.3. Hot flush treatments

75% of women consult their GP about the menopausal symptoms (Hope et al., 1998). In the UK treatment is offered by a variety of healthcare professionals (doctors, nurses, gynaecologists and endocrinologists) of whom 1,600 belong to the British Menopause Society (BMS), a society dedicated to advancing education in all matters related to the menopause http://www.thebms.org.uk/about.php (accessed 21.8.08).

3.3.1 Treatment prior to 2002

The BMS produces a practical guide[14] for clinicians for the management of the menopause which are published in the BMS Handbook (2002) written by UK experts in the field – endocrinologists, gynaecologists, and menopause specialist doctors. It also regularly sends its member an 'Integrated healthcare pathway for the menopausal woman' booklet drawn from the handbook. The 2002 BMS Handbook describes HRT as the treatment of choice for the menopause and lists three different types of treatment: Oestrogen based Hormone replacement therapy preparations (HRT), Non oestrogen based treatments and Complementary & Alternative therapies. The benefits of HRT – both projected/theoretical and evidence based – for vasomotor symptoms, (and a wide range of other chronic diseases) occupy 44 pages compared to 2 pages on non oestrogen based treatments and 5 pages on complementary and alternative therapies for vasomotor symptom control. These benefits are summarised below.

Oestrogen based Hormone replacement therapy preparations

There are at least six different types of oestrogen and progestogens available which can be delivered in a variety of ways – orally via tablets, transdermally via patches or a gel or slow release percutaneous implant, intravaginally via creams, tablets, rings and pessaries, or nasally via sprays. Oestrogen only HRT is prescribed for women who have had a hysterectomy: others are generally prescribed combined HRT (oestrogen with a progestogen) to prevent endometrial hyperplasia. In the UK in 2001, 50% of all women aged 50-64 had tried HRT and 33% were currently using HRT (Million Women Study Collaborators, 2003).

Non oestrogen based treatments

As well as oestrogens and progestogens, other types of hormone preparations such as tibolone and androgen therapy can be used for the treatment of hot flushes. Tibolone is a synthetic steroid compound with weak oestrogenic, progestanic and androgenic actions. Androgen therapy is provided in the form of testosterone implants. These may be used to improve libido but are not successful in all women. Clonidine (a neuroendocrine agent) and Selective Serotonin Reuptake

---

[14] The Royal College of Obstetricians & Gynaecologists (http://www.rcog.org.uk/ accessed 22.8.08) do not produce 'Menopause' guidelines

Inhibitors (SSRIs) such as Venlaflaxine, paroxetine and fluoxetine are also sometimes used but have limited success and the side effects are often not well tolerated.

Complementary and alternative therapies

The BMS Handbook (2002) lists six different types of complementary and alternative therapies: Phytoestrogens (plant substances structurally or functionally similar to oestradiol and are found in many foods), Herbalism (Black Cohosh, St John's Wort and Ginseng), Dehydroepiandrosterone (an adrenal steroid), Progesterone transdermal creams, Other complementary therapies: Alexander technique, Ayurveda, Osteopathy and Reiki, Diet and lifestyle modification and Counselling

3.3.2 Significant events in 2002/3

Between July 2002 and August 2003 the results of two randomised controlled trials (RCTs) and one observational study were published in the UK and USA. The two randomised controlled trials (RCTs) observed the effect of both combined and oestrogen only HRT compared to placebo and included a total of 19,371 women aged 50 plus. The observational study observed 1,084,110 women. Each of these three studies is described more fully below.

WHI: The USA Women's Health Initiative (Writing Group for the Women's Health Initiative Investigators, 2002) was a double blind randomised controlled trial of 16,608 asymptomatic women aged 50 – 79 and was the largest trial of HRT ever conducted. In July 2002 the combined HRT (estrogen+progestin) arm of the trial was stopped prematurely due to the high number of cases of invasive breast cancer, strokes and CHD in the estrogen+progestin arm. Post menopausal HRT appeared to be associated with an increased risk of coronary heart disease, stroke, breast cancer, venous thrombolic events, dementia and gall bladder disease.

HERS and HERS II: The Heart and Estrogen/progestin Replacement Study (HERS) was a randomised, double blind, placebo controlled trial of 4.1 years duration (Hulley et al, 1998) and subsequent open-label observational follow up for 2.7 years (HERS II) (Grady et al., 2002) of 2,763 women with coronary heart disease and an average age at enrolment of 67 years. The aim of the HERS trial was to examine the effect of long-term postmenopausal combined HRT on thromboembolic events, biliary tract surgery, cancer, fracture and total mortality. In July 2002 the results were reported that treatment for 6.8 years with combined HRT in older women with coronary disease increased the rates of venous thromboembolism and biliary tract surgery, and did not produce the expected favourable trends in overall rates of Cardio Vascular Disease (CVD), fractures or death.

MWS: The UK based Million Women Study (MWS) observational study (Million Women Study Collaborators 2003) was set up to investigate the effects of specific types of HRT on incident and fatal breast cancer. During 1996-2002, 1,084,110 UK women aged 50-64 were recruited

through the NHS Breast Screening Programme. The year after the publication of the results of the HERS and WHI trials, the MWS reported an increased risk of breast cancer for women taking HRT, both the incidence of invasive breast cancer (relative risk 1.66) as well as mortality from breast cancer (relative risk 1.22). Users of combined HRT had a higher relative risk of invasive breast cancer than users of oestrogen only HRT (relative risk 2.0 vs 1.3). The relative risk of breast cancer increased as early as one year after the start of HRT (1.74) and increased to 2.17 for those who had used it for 5-9 years, and 2.31 for those who had used it for 10 years plus.

3.3.3   Treatment post 2002/3

Publication of the results of these three studies widely impacted on the actions of research funders, patients and clinicians. In October 2002, as a consequence of the findings and early stopping of the WHI, the MRC decided to stop the Women's International Study of long duration Oestrogen after Menopause (WISDOM) one year into the trial (White, 2002). This RCT was set in general practices in the UK, Australia and New Zealand and aimed to study the effects of combined HRT vs oestrogen only HRT vs placebo in 22,300 postmenopausal women aged 50 – 69 over ten years. These three studies led to the prescribing guidelines of the Government Committee on Safety of Medicines and The Royal College of Obstetrics & Gynaecology advised in December 2003 that HRT should not be used as a first line therapy for the prevention of osteoporosis as the risks outweighed the benefits. In 2004 the BMS altered their clinical guidelines for HRT stating that HRT was not recommended for longer than 5 years in the over fifties and that the primary indication for systemic HRT was the relief of moderate to severe vasomotor symptoms only. As a result of these recommendations, clinicians began to encourage postmenopausal women without vasomotor symptoms to stop HRT and to limit its use to short term treatment for menopausal symptoms (Grady et al, 2002).

In the immediate aftermath of the publicity surrounding these studies, many women (estimates vary from 48%-77%) either decided to stop taking HRT themselves or were advised by their GPs to do so (Ness et al., 2005). Clinicians and women started asking how they should stop HRT but there had been no studies of the best way to stop HRT. However, a cross sectional survey (Ockene et al., 2005) of 8,405 women from the WHI RCT who stopped combined HRT found that women randomised to HRT were 4 to 7 times more likely to report vasomotor symptoms after discontinuing the study pills than those randomised to placebo – indicating an issue with withdrawal from HRT.

3.4.   Learning lessons from the evidence: implications for research

The earliest RCTs of HRT were published in 1953 (e.g. Blatt et al., 1953) yet it has taken fifty years for the type and extent of the risks of HRT to be known. As a clinician/researcher commented in the Lancet:

"How has it been possible to reach this point in healthcare provided to middle aged women? More than 50% of the post menopausal women in the Million Women Study use or had used, a preventive therapy whose safety must now be questioned. Despite stringent modern control of drugs, how has heavy promotion of HRT put millions of women at risk?" (Lagro-Janssen et al., 2003).

This section addresses the question as to why HRT randomised controlled trials (RCTs) have not identified this information earlier by examining a Cochrane systematic review and meta-analysis of oral[15] oestrogen replacement therapy versus placebo for hot flushes (MacLennan et al, 2002) which summarises the RCT evidence prior to 2002/3 in this area.

The objective of this particular systematic review was to examine the effect of oral HRT compared to placebo on vasomotor symptoms. The review identified 21 placebo trials with 2,511 participants in total with a mean age of 50 years. However, the data from 6/21 of studies was unsuitable for inclusion in meta-analyses. The majority of studies recruited healthy menopausal women from clinical settings (mostly menopause clinics). Two trials excluded women with severe vasomotor symptoms. RCTs were short term (majority of trials 15/21 were 6 months or less, with the longest trial lasting 36 months). Half of these RCTs (12/21) had been published in the 1970s and 1980s. Only 2/21 trials clearly used an 'Intention To Treat'[16] (ITT) analysis and significant losses to follow up were reported: 5 trials – less than 10% loss to follow up, 8 trials – 10-20%, 7 trials - 20 to 30%. Recurrent reasons for withdrawals from the HRT arms were irregular bleeding, breast tenderness, oedema, joint pain, nervous/psychiatric problems, but there were no reports of any serious adverse events. Failure to conduct an ITT analysis may have underestimated the number of side-effects if these were the reasons for withdrawal in the participants not followed up. Thus some of these trials performed analyses which were subject to reporting and ascertainment bias (MacLennan et al., 2002). This meta-analysis showed a strong positive effect for HRT. Withdrawal due to early onset adverse events was not significantly increased for HRT (OR 1.38, 95% CI 0.87, 2.21) with reviewers concluding that: '*HRT is a highly effective therapy for the treatment of hot flushes and night sweats and its effect was sustained in trials of three months to three years duration…' (MacLennan et al., 2002).*

Despite HRT trials being conducted since 1953, the nature of the risks associated with HRT was not fully discovered until 2002/3. The methodological reasons for this are three fold. Firstly, there are issues with regards to the pre 2002/3 trials not using an ITT analysis, despite over 10% of withdrawals being reported. These issues are now being addressed as journals require trial reports to use CONSORT reporting guidelines (www.consort-statement.org) which includes the reporting of the flow of participants through each stage and number of participants in each group included in each analysis' and whether the analysis was an ITT analysis

---

[15] The most common method of taking HRT

[16] 'Intention To Treat' (ITT) analysis is where all patients, whether they complied with the intervention or not, are included in the analysis according to their original study group (Saks & Allsop p.237)

The second issue was that both RCTs and observational studies (e.g. Pettiti, 1998 in MacLennan et al., 2002) were of women who were healthier and younger than the women requesting treatment for menopausal symptoms. Thus the data was derived from populations which *'could differ substantially from the individual being treated'* (Hickey et al., 2005). The third issue is that trials were of short duration and looked only at early onset side effects. Thus though the results were not statistically significant at 3 years or less (MacLennan et al., 2002), at 6.8 years (HERS II) they were statistically significant.

3.5   Lessons for appropriate clinical trial design

From the perspective of the example of the condition chosen, menopausal hot flushes, the implications for further research are two fold. Firstly, future research should be conducted in populations that are representative of the 'with need' population, so that the findings will be generalisable to the 'with need' population. The second implication is that future research should produce long term[17] as well as short term outcomes so that the long term safety and effectiveness of treatments can be assessed rather than predicted (Box 3.1).

Box 3.1   Key Criteria III and IV

III   Have findings that can be generalised to the 'with need' population
IV   Produce short and long term outcomes

3.6   Alternative treatments to HRT

3.6.1   Size of the problem

It had been known for some time that some women were unable to take HRT (contra indications being a history of breast cancer or venous thromboembolic disease) but with the publication of the three studies and the changed guidelines, some women now seemed to either not want HRT, or be recommended to stop HRT by their clinicians. Nationally, surveys of doctors, consultants & patients also reported a significant number of women stopping HRT (Ness et al., 2005; Ettinger et

---

[17] Where researchers yield to the temptation to study short term outcomes rather than more important long term outcomes Jadad (2007) describes as 'time term' bias

al., 2003)[18]. However there were no population based estimates of the numbers of women who could not or would not take HRT or what non HRT interventions/treatments they were using. Thus there was a need to assess the size of the problem using a population based survey of women and understand more about the non HRT treatments women were using.

3.6.2   Non HRT treatments

After the events of 2002 and 2003 there was an increase in interest in CAM type non HRT treatments. The 2005 & the 2002 BMS Handbook both listed the same treatments but with the addition of homeopathy in 2005. The 2006 BMS 'Integrated healthcare pathway for the menopausal women in primary care' included a section on alternative & complementary therapies'.

Also, several USA surveys and reviews on CAM were published around 2002/3. A telephone survey (Keenan et al., 2003), of 2,602 women aged 45+ in the USA reported that 62.9% of these women reported hot flushes and 46% of the total number of women (2,602) were using CAM but there was no information on how many of these CAM treatments were being used to treat menopausal hot flushes. Another population based survey of women aged 45-65 conducted in the USA (Newton et al., 2002) found that a higher percentage (76.1%) were using one or more of eight alternative therapies. Newton et al. (2002) reported that 22.1% of women were using one or more of these alternative therapies to manage menopause symptoms (stress managements 9.1%, over the counter alternative remedies 13.0%, chiropractic 0.9%, massage therapy 2.6%, dietary soy 7.4%, acupuncture 0.6%, naturopath or homeopath 2.0%, herbalist 1.2%). By 2005 there were still no UK population based surveys that described which treatments women were using since the publication of the three studies. Thus there was a need to consider the treatments women were using in the UK.

3.6.3   Effectiveness and safety of non HRT treatments

Non oestrogen based (pharmaceutical) treatments: According to the BMS (2005), Tibolone and Androgen therapy have similar effectiveness to oestrogen based HRT, and Clonidine is moderately effective compared to placebo in the treatment of hot flushes. Selective Serotonin Reuptake Inhibitors (SSRIs) have been subjected to clinical trials of short duration (4 - 6 weeks) with results that show a reduction in hot flushes over placebo, however their medium term effectiveness is unknown. Tibolone has similar risks to oestrogen based HRT, Androgens can produce adverse effects such as weight gain, bloating, hirsutism and acne. Clonidine is associated with adverse events in 10 – 50% of patients. The safety of SSRIs is unknown and there are adverse effects in about 20% of patients resulting in the discontinuation of SSRIs (Hickey et al., 2005; Stearns et al., 2002).

Complementary & alternative therapies: The BMS (2002, 2005) states that there was only poor evidence from RCTs that these therapies improve menopausal symptoms, a view echoed

---

[18] Locally, in the NHS Sheffield Menopause/PMS clinic, by early 2003, the number of referrals to the homeopathy service had tripled with the majority of women reporting severe and/or frequent hot flushes and not wanting to take HRT (Relton, 2005).

in reviews of treatments for menopausal symptoms (Hickey et al., 2005) which concluded that *'there is not enough evidence that any of the complementary therapies available are any better than placebo for menopausal vasomotor symptoms, and few safety data exist'.* Reviews of treatments for menopausal symptoms (Stearns et al., 2002) often only included herbs and food supplements in their review of complementary medicine, thus ignoring acupuncture, osteopathy, chiropractic, homeopathy, massage therapy etc. Two reviews (Kronenburg et al., 1994; Huntley & Ernst, 2002) focussed specifically on CAM treatments for menopausal symptoms. Kronenburg et al., (2002) concluded that clinical trials do not support the use of CAM therapies or herbs, although Black Cohosh and foods containing phytoestrogens showed promise. Huntley et al., (2002) reported weak evidence for a variety of herbal treatments (Black Cohosh, Kava, Ginseng, Dong quai, Evening Primrose Oil, St John's Wort, Vitamin E) but there were questions regarding the safety of all of these treatments. There was also weak evidence for food supplements (soy & phyto-oestrogens), acupuncture, relaxation and spinal manipulation but no safety concerns reported. This review concluded that there is no 'compelling evidence' for the efficacy of any CAM treatment for alleviating menopausal symptoms

3.6.4 Homeopathy

A recent audit of patients receiving treatment from medically qualified homeopaths at the five NHS homeopathic hospitals found that menopause was the third most common reason for patients to have treatment (Thompson et al., 2008). A systematic review of homeopathy for pre menstrual syndrome (PMS) and the menopause (Relton, 2004) identified four menopause observational studies of treatment by a homeopath (Clover & Ratsey, 2002; Thompson & Reilly, 2003, Thomas & Strong, 2001; Relton & Weatherley-Jones, 2005) and two menopause 'homeopathy' RCTs (Thompson et al., 2005; Jacobs 2005). This section briefly reports the findings of this systematic review.

Observational studies

Two observational studies reported the outcomes of patients treated at two NHS homeopathic hospitals (Clover & Ratsey, 2002; Thompson & Reilly, 2003). There were also two audits (Thomas & Strong, 2001; Relton & Weatherley-Jones, 2005) of outcomes of patients in an NHS community menopause clinic, these audits included patients with PMS symptoms as well so are not described here. All patients were treated by homeopaths using individualised homeopathy. All the study patients had one or more of the following menopausal symptoms: hot flushes, vaginal dryness, mood disturbance, fatigue. The patients in Thompson & Reilly (2003) study all had a diagnosis of breast cancer and the Clover & Ratsey, (2002) study included significant numbers of women with a diagnosis of past or current breast cancer (20/31). Many women in the studies were taking a wide medication: tamoxifen, HRT, antidepressants, clonidine, and chemotherapy. Each study used patient assessed outcomes as their primary outcome but neither

study used a validated outcome measure. Clinically significant improvements were reported by Clover & Ratsey (2002) for hot flush frequency and severity, and Thompson & Reilly (2003) reported clinically significant improvements in: effect of symptoms on daily living, mood, and quality of life.

Randomised controlled trials

Both RCTs were double blind placebo-controlled and were conducted in hospital settings in the UK (Thompson et al, 2005) and the USA (Jacobs et al., 2005). Duration of the intervention varied between 16 weeks (Thompson et al., 2005) and 6 – 12 months (Jacobs et al., 2005). Sample sizes were 83 (Jacobs et al., 2005) and 53 (Thompson et al., 2005). Both RCTs used repeated consultations with a homeopath with either an individualised homeopathic remedy or placebo, however, Jacobs et al., (2005) had an additional treatment arm of a combination homeopathic remedy. Inclusion criteria for both trials were: three or more hot flushes a day and a history of breast cancer. Exclusion criteria for both trials were: severe concurrent chronic health problems, undergoing chemotherapy, radiation or surgery. The patient mean age was 52 (Thompson et al., 2005) and 55 (Jacobs et al., 2005) and use of Tamoxifen was high (80% Thompson et al., 60% Jacobs et al.). Jacobs et al. reported a higher dropout rate (28/83) than Thompson et al., (5/53) this can be attributed to the greater length of the Jacobs trial (3 times longer) and perhaps the older age group.

Jacobs et al. used a direct primary outcome – hot flash[19] severity score (a combination of frequency and severity of hot flashes as recorded in patients symptom diaries). Thompson et al. used two indirect primary outcomes derived from a validated patient generated outcome measure MYMOP.

Neither of the two RCTs (Thompson et al., 2004; Jacobs et al. 2005) showed a statistically significant improvement in the primary outcome measures for 'homeopathy' over placebo. Jacobs (2005) did however produce a positive trend for homeopathy in the reduction of hot flashes during the first three months ($p=0.1$) and a reduction in the Kupperman Menopausal Index ($p=0.1$) at one year. Both these studies had a high methodological assessment score. This systematic review concluded that:

> *"There is only low level evidence of the effectiveness of homeopathy for women with menopausal symptoms especially hot flushes. However for women with a diagnosis of breast cancer suffering from hot flushes (and other symptoms of oestrogen withdrawal), there are very few safe and effective treatment options." (Relton, 2004)*

3.6.5   Implications for future research in non HRT treatments

Despite RCT evidence of effectiveness for pharmaceutical type non oestrogen based treatments (e.g. tibolone, SSRIs) there were issues regarding side effects and the long term safety of these treatments. CAM treatments appeared popular with women, but many RCTs of hese treatments suggested that they were no better than placebo. However, a small number of CAM treatments

---
[19] Flash is the American equivalent of the English term 'flush'

had RCTs that showed some effectiveness in the treatment of hot flushes (Soy products, herbal combinations, acupuncture and relaxation). The two RCTs of homeopathy were inconclusive as to effectiveness but observational evidence suggested that treatment by a homeopath was associated with beneficial outcomes and there were no concerns over the safety of homeopathic remedies. The systematic review stated that the implications for 'homeopathy' research were that:

> *"Homeopathy is a highly individualised strategy that is difficult to study within the traditional framework of randomised double blind controlled trials. However the included studies show some interesting results and as such warrant further research. Further research would be made more informative by examining homeopathy as a whole intervention and not separating the consultation from the remedy. Comparative pragmatic trials (non-blinded) with randomisation may be a better framework for studying the possible effectiveness of individualised homeopathic treatment for PMS and menopause symptoms in both. Replication of trials and larger trials (sufficiently powered trials) are also needed"(Relton, 2004).*

The conclusion was that the safety and effectiveness of CAM treatments needed to be further explored, in particular treatments provided by the NHS such as treatment by a homeopath.

3.7   Conclusion

3.7.1   Future research

This chapter identified two key criteria for clinical trial design which provides information needed to make decisions about the provision of homeopathy in the NHS when taking the perspective of a particular condition: menopausal hot flushes. These two key criteria (III and IV) have been added to key criteria (I and II) derived from the perspective of the condition: homeopathy in the NHS to give four key criteria for appropriate clinical trial design (Box 3.2).

Box 3.2   Key Criteria I – IV

I   Pragmatic RCTs
II   Allow the complexity and proper functioning of intervention
III Have findings that can be generalised to the 'with need' population
IV Produce short and long term outcomes

3.7.2   HRT

There have always been women with menopausal hot flushes for whom HRT was contra indicated and after the publication of the three studies (MWS, HERS & WHI) during 2002/3, and the subsequent changes in clinical guidelines, there was an increase in the proportion of women who could not take HRT. Thus there were a significant number of women with

menopausal hot flushes who could/ would not take HRT, that is, women with an unmet need. There is a need to look at the level of need for alternatives to HRT and to understand what types of treatments women are using since 2002/3.

3.7.3   Homeopathy

Observational studies report significant benefit in hot flushes and general health outcomes for women who cannot or will not take HRT. Nationally, the NHS provides homeopathic treatment for women with menopausal hot flushes in a variety of settings (homeopathic hospitals, community clinics, GP surgeries). The evidence of clinical and cost effectiveness of treatment by a homeopath for the treatment of menopausal hot flushes thus needs to be established.

Chapter 4

The patient perspective on clinical trial participation

4.1   Introduction

In the search for an appropriate clinical trial design this thesis has identified the need for a pragmatic RCT that retains the complexity and proper functioning of the intervention and produces long as well as short term outcomes that are generalisable to the 'with need' population. Moreover, the examples used to illuminate this search, revealed a need for a pragmatic RCT of the clinical and cost effectiveness of homeopathy for women with menopausal severe/frequent hot flushes.

Further insight into appropriate clinical trial design might be gained from exploring two further perspectives: the individual patient's perspective on clinical trial participation and the perspective of scientists who design and critique clinical trials. The rationale for separating out the perspective of the patient from that of the scientist is that each may have different motivations. In participating in clinical research the primary motive of the scientist (in the area of Health Services Research) is to obtain *data* to be used to benefit *all* patients with condition X (in the *future*); whereas the primary motive of the individual patient participating in a clinical trial may perhaps be to receive the *best treatment* for *themselves* with condition X (preferably *now).* If there are different motives then these will be associated with different values, expectations, behaviours and perspectives; and thus possibly different key criteria for appropriate trial design.

4.1.1   Aim & objectives
The aim of this chapter is to identify key criteria for an appropriate pragmatic RCT design from the individual patient's perspective on participating in clinical trials. The objectives of this chapter are to:
- explore the literature as to why patients do enter clinical trials

- explore the literature as to why patients do not enter clinical trials

- examine current NHS Informed Consent procedures for clinical trials

- explore the patient perspective on NHS Informed Consent procedures

- discuss the patient's experience of recruitment processes and the ethics of current NHS Informed Consent procedures

4.2.   Why <u>do</u> patients enter clinical trials?

4.2.1   Opting in

As a result of the Data Protection Act of 1998 and NHS Information Governance (www.connectingforhealth.nhs.uk), researchers cannot approach patients directly to participate in research, instead the researcher must approach the current (or last treating) clinician who (if they believe the request is appropriate) may then approach the patient to ask if the patient wishes to participate in the research. Only those patients who respond positively to this request may then be contacted by the researcher. In short, patients have to 'opt in' to rather than 'opt out' of research. The next step for the researcher is to obtain 'Informed Consent' from those patients who express an interest in 'opting in'[20]. Participating in a clinical trial is thus viewed as being contingent to an individual patient's relationship with their current clinician. However, RCTs are designed to help patients collectively in the future rather than each individual patient now, this section explores some of the literature as to why individual patients do enter clinical trials.

4.2.2   Methods

There has been no systematic literature review published on why patients do enter clinical trials. Rather than perform an extensive literature search of this area, this thesis examines a commonly held assumption as to why patients enter clinical trials: that patients enter clinical trials because they are motivated by altruism[21] (the selfless concern for the welfare of others which is seen as a virtue in Western culture). For example the International Committee of Medical Journal Editors states that:

> *"Altruistic individuals volunteer for research because they trust that their participation will contribute to improved health for others"*
> http://www.wame.org/wame-listserve-discussions/clinical-trials-registry accessed 20.8.08

Yet qualitative research by Heaven et al. (2006) has found that patients in RCTs do not just view themselves as volunteers but have a range of identities with 'volunteers' on one end of the

---

[20] Research indicates that an 'opt out' system produces higher recruitment rates and a more representative population (Junghans, 2005)

[21] In the genome and biobank debates, altruism is sometimes described as 'genetic solidarity'.

spectrum and 'patients' at the other end. Heaven et al. reports that those who identified themselves as 'patients' were more likely to describe their reasons for participation as personal benefit rather than altruism. The assumption that the main reason why patients enter clinical trials is altruism is explored through a review of the relevant literature reporting empirical findings.

On 28.12.07 the Medline database from 1950 – 2007 was searched combining the search terms 'altruism' and 'RCT$/trial$'. What follows is a narrative summary, with commentary, of a search of the Health Services Research literature to answer the question: 'Is altruism the main reason why patients enter clinical trials?'. Twenty four references were identified of which 13 were excluded. Reasons for exclusion were: duplicated article (1), no abstract available online (2), altruism not related to trial participation but to the supposed effect of the intervention (1), no information on motives for participation (9). Eleven articles were included (Table 4.1)

4.2.3   Characteristics of the articles included

All studies were published after 2001 (perhaps indicating increasing interest in this question) with the majority of articles reporting the results of research conducted in the USA (6) with the rest conducted in the UK (2), Canada (2) and Denmark (1). The trials were conducted in a variety of conditions with some being prevention trials and other intervention trials. Numbers of people studied ranged from 11 to 475.

Three articles reported studies of participants and non participants (accepters & decliners), five articles reported studies only of participants and three articles reported studies of patients who had been approached for a hypothetical trial.

All studies used information derived either from patient questionnaires or semi structured interviews. Six studies used open questioning methods and five used closed questioning methods. Patients who were asked closed questions had to express their agreement or disagreement with a variety of statements constructed by the researchers. Statements included both altruistic and non altruistic reasons for participation. Some studies asked for agreement or disagreement, others asked patients to state whether they strongly agreed, agreed, disagreed or strongly disagreed with each statement.

In understanding the literature it is helpful to categorise the types of benefits reported. King et al., (2000) offer a helpful typology which was applied to the 11 included studies (Table 4.1). This typology identifies three potential types of benefit from being a research participant:

- **Direct benefit** from receiving the intervention under study (e.g. money, access to particular treatment) – available to study patients who are allocated to the study intervention
- **Indirect benefit** from participating in a clinical trial (e.g. academic medical setting, close monitoring) – available to all study patients
- **Aspirational or altruistic benefit** related to what will be learned as a consequence of the research.

Table 4.1 (Patients and clinical trials: reasons for participation) reports those studies which used closed questions first and then those studies which used open questions.

4.2.7   Results: Closed question studies

Closed question methods were used by five studies (Madsen et al. 2002, Rojavin et al. 2006, Gabbay & Thomas 2004, McLeod et al. 2004, Criscione et al. 2003). These studies asked different questions using different statements and are thus hard to summarise, or discern patient's reasons for participation, for example Gabbay & Thomas state that 85% of participants 'considering the research to be important' – but provide no clarity as to how or from whose viewpoint the term 'important' is defined. Crisicione et al. (2003) report that the statement that elicited the highest agreement was 'being in this trial gives me hope' (99%) but again it is unclear whether it is personal hope (for the individual) or universal hope (for mankind in general or for science).

Two closed question studies reported their findings in a way that illuminates this discussion on motivation (Rojavin et al. 2006, Madsen et al. 20002) with both studies reporting that direct benefits received higher scores compared to altruism. Rojavin et al. (2006) used a 'Patients' Expectations, Attitudes and Knowldege' (PEAK) questionnaire with a five point Likert scale and this study reported that the motivating factor that received the highest score (4.33) was interest in receiving the investigational product. The possibility of getting skilled professional care scored 4.07 and altruism scored 3.89. Madsen et al. (2002) reported that direct & indirect benefits were rated as important or very important by 86% and 89% of Irritable Bowel Disease trial patients respectively, and altruism was rated as important or very important by 84% of patients. Similar percentages were reported for cancer trial patients.

4.2.8   Results: Open question studies

There were six articles that reported the results of studies using open question methods. Three of these studies reported their findings using quantitative data (Rosenbaum et al. 2005, Halpern et al. 2003, Rodger et al. 2003). The evidence from these three studies was that altruism is not the most commonly reported reason for participation, however two of these studies were of hypothetical rather than actual trials.

Rosenbaum et al. (2005) sought to determine whether altruism as a reason for participation in research is independently associated with adherence to a medical regimen in a clinical trial and found that under half (45.7%) of participants provided at least one altruistic reason for participation and a fifth (20.6%) gave an altruistic reason as their only reason for participation. Halpern et al. (2003) reported the most commonly cited motivations for participation in a hypothetical trial were 'personal': personal health benefit (40%), access to care (12%), money (6%) (i.e. 'direct' or 'indirect' benefits). The most commonly cited non personal motivations cited were: altruism (37%) and to contribute to scientific knowledge (14%) (which King et al. describes as 'aspirational or altruistic benefits'). Rodger et al. 2003 reported that the most

Table 4.1			Patients and clinical trials: reasons for participation					
Author Year **(Country)**	**Title of article**	**Type of patient**	**Clinical condition**	**Number of patients**	**Questions**	**Reasons for participation**	**Main reason for participation**
Criscione et al. 2003 (USA)	Informed Consent in a clinical trial of a novel treatment for rheumatoid arthritis	Participants	Rheumatoid arthritis	30	Closed	Being in this trial gives me hope & to help other patients with RA (99%)	Direct benefit
Madsen et al. 2002 (Denmark)	Attitudes towards clinical research amongst participants and non participants	Participants & non Participants	Cancer trials	41/47	Closed	Access to new drug Being closely monitored To help future patients	Direct benefit
McLeod et al. 2004 (Canada)	Women's views regarding participation in a proposed RCT of twin delivery	Participants in a hypothetical trial	Pregnant mothers with a known twin gestation	64	Closed	Most common agreement to participation was altruism (n=28)	Altruism
Rojavin et al. 2006 (USA)	Factors motivating dyspepsia patients to enter clinical research	Participants	Dyspepsia	247	Closed	1. To receive treatment 2. Get skilled professional care 3. Altruism	Direct & indirect benefit
Gabbay & Thomas 2004 (UK)	When free condoms and spermicide are not enough: barriers and solutions to participant recruitment to community-based trials	Participants & non participants	Condom & additional spermicide trial	303	Closed	Considering the research important (85%) Wanting to help the researchers (70%) Having time to help (62%) Getting free condoms & lubricant (56%)	Not stated

Eng et al. 2005 (Canada)	Understanding participation in a trial comparing cryotherapy and radiation treatment	Participants & non participants	Prostate cancer	11	Open	Participators participated principally in the hope of getting cryotherapy treatment	Direct benefit
Heaven et al. 2006 (UK)	Patients or research subjects? A qualitative study of participation in a randomised controlled trial of a complex intervention	Participants	RCT of decision support tools	31	Open	The majority hoped to benefit to some degree from participation & a primary desire to contribute to advancing medical practice and the wellbeing of others	Not reported
Rosenbaum et al. 2005 (USA)	Altruism as a reason for participation in clinical trials was independently associated with adherence	Participants	Estrogen for stroke	475	Open	45.7% gave at least one altruistic reason for participation 20.6% only gave an altruistic reason for participation	Direct & indirect benefit
Villarruel et al 2006 (USA)	Recruitment and retention of Latino adolescents to a research study: lessons learned from a RCT	Participants	Reducing HIV sexual risk behaviour	106	Open	Four main facilitator patterns emerged: peer/family support, program incentives, commitment and a desire to help	Not reported
Rodger et al. 2003 (USA)	Participation of pregnant women in clinical trials; will they participate and why?	Participants in a hypothetical trial	Pregnant women	50	Open	Potential benefit to fetus (68%) Benefit to personal health 27%) Altruism (5%)	Direct & indirect benefit
Halpern et al. 2003 (USA)	Hypertensive patients willingness to participate in placebo controlled trials: implications for recruitment efficiency	Participants in a hypothetical trial	Hypertensive patients	126	Open	Personal health benefits (40%) Helping other patients (37%) Contributing to scientific knowledge (14%) Access to care (12%) Money (6%)	Direct benefit

important determinants of pregnant women's willingness to participate in a hypothetical clinical trial were: potential benefit to fetus (68%), benefit to personal health (27%), and altruism (5%).

4.2.9   Comparison of closed and open questions

Of the studies which do report the main reason given by patients for trial participation, three out of four closed question studies report direct/indirect benefit as the main reason for participation and all four open questions studies report direct/indirect benefit as the main reason for participation. Two studies both sought to gain information regarding pregnant women's views on participation in trials (McLeod et al. 2004, Rodger et al. 2003) using two different methods and interestingly drew two different conclusions. Using open questions, Rodger et al. (2003) reported that 5% of women gave altruism as a reason to participate in a hypothetical trial. Using closed questions, McLeod et al. (2004) reported altruism as the main reason for participation. One possible explanation of this difference is that the closed question study design may have influenced the mothers to give socially acceptable reasons (altruism) instead of personal reasons (direct/ indirect personal benefit).

4.2.10   Discussion

Three out of eleven studies did not state the main reason for participation, but of the eight studies that reported reasons for participation, seven studies reported either 'direct' or 'direct and indirect' benefits as being the most commonly given reason for participation in clinical trials. It is possible that the findings of this review may have been affected by the healthcare context in which the research reported in this literature was conducted. Two of the studies were conducted in the UK, (Heaven et al., 2006; Gabbay & Thomas, 2004), one in Denmark (Madsen et al., 2002) and two in Canada (McLeod et al.: Eng et al., 2005) and five of the studies were conducted in the USA (Rojavin et al. 2006; Criscione et al, 2003;Rosenbaum et al., 2005; Halpern et al., 2003; Rodger et al., 2003) where there is less publicly provided healthcare free at point of delivery and thus perhaps greater unmet healthcare needs than in the UK, Canada & Denmark where publicly funded healthcare systems provide healthcare free at point of delivery.

Neither of the two studies conducted in the UK (Heaven et al., 2006; Gabbay & Thomas, 2004) reported the main reason for participation by patients. But the three studies conducted in Denmark and Canada (Madsen et al., 2002; McLeod et al., 2004; Eng et al., 2005) which did report the main reason for participation, report conflicting findings. McLeod et al. state altruism as the main reason but Madsen et al. and Eng et al. both report either direct or direct and indirect benefit as the main reasons for participating in trials by patients.

The four studies conducted in the USA which did report the main reason for participation, all reported direct benefits.

The evidence from this literature review is congruent with the hypothesis that the primary motive or aim of the individual patient is to receive the *best treatment* for themselves for their

condition (X). Another way of testing this hypothesis is to examine why patients do not enter clinical trials. If patients do not enter clinical trials because they believe that they will not receive the best treatment for themselves now – then this would support the above hypothesis. The next section asks the question 'why don't patients enter clinical trials'?

4.3.   Why <u>don't</u> patients enter clinical trials?

4.3.1   A systematic review

The literature on why patients do not enter trials is considerably more extensive than the literature on why patients do enter trials. The literature up to 1996 is covered in a comprehensive systematic review on why patients don't enter trials: *'Barriers to participation in RCTs: A systematic* review' (Ross et al., 1999). This systematic review identified 78 articles published between 1986 and 1996 which reported findings relating to problems with recruitment of clinicians or patients to clinical trials and which reported either empirical quantitative or qualitative data. This review reports eight types of barriers to patient participation in trials (Table 4.2). Ross et al. (1999) divides these into two main categories: 'Patient concerns' and 'Clinician as barrier to patient participation'.

4.3.2   'Patient concerns'

The category 'Patient concerns' reports the following types of barriers: patient concerns about information and consent (33%), additional demands on the patient (26%), patient preferences for a particular treatment (or no treatment) (19%), worry about uncertainty of treatment or trials (12%). Patient concerns about information and consent was the most commonly reported barrier and Ross et al. report a variety of patient concerns: patients wanted more information, concerns about the consent process (three studies reported that providing information reduced recruitment rates), and the purpose of the consent form was unclear to some patients.

4.3.3   Location of research

The majority of studies (n=39) were conducted in cancer patients and in the USA (n=48). Only 10 studies from the UK were included. As was mentioned earlier, since the bulk of the US healthcare system is not free at point of delivery, patients often participate in research in order to obtain free treatment – this is much less the case in the UK and Europe. In order to see if the location of the research affected the reported findings, information from 26 studies that were conducted in the USA (refs 7 – 33 & 79-80 in Ross et al.) was removed to obtain information from studies conducted in countries where healthcare is free at point of delivery (Europe & Canada), but similar results were found.

Table 4.2   Barriers to patient participation in RCTs (Ross et al., 1999)

Barrier	Studies from all countries N=78	Non USA studies N= 52
Patient concerns		
Additional demands on the patient	21 (26%)	
1. Additional procedures and appointments	13 (16%)	2 (4%)
2. Travel problems and costs	8 (10%)	3 (6%)
Patient preferences for a particular treatment (or no treatment)	15 (19%)	9 (17%)
Worry about uncertainty of treatment or trials	9 (12%)	4 (8%)
Patient concerns about information and consent	26 (33%)	10 (19%)
Clinician as barrier to patient participation		
Protocol causing problem with recruitment	13 (16%)	6 (11%)
Clinician concerns about information provision to patients	7 (9%)	2 (4%)
Clinician influencing patient decision not to join	6 (8%)	3 (6%)

4.3.4   Discussion

The examination of the 'altruism and trial' literature as to why patients do participate in trials reveals that most patients participate in trials primarily to gain direct and/or indirect benefits rather than from altruistic motives; and the literature on why patients do not participate in clinical trials shows a variety of barriers for patients. Indeed, these two findings may be related, as barriers to trial participation may also be barriers to obtaining the direct and indirect benefits for the patient.

The extensive literature depicts a complex picture as to why patients do not participate in clinical trials with *'Patient concerns about information and consent'* being the most frequently reported barrier to participation. 'Informed Consent' is a vital part of the process by which patients are recruited to clinical trials, yet *'Patient concerns about information and consent'* is the most commonly reported barrier. In routine healthcare however, there are few issues with regards to recruitment, or information or consent. Thus one possible solution to *'Patient concerns about information and consent',* is for clinical trial processes to replicate the processes of routine healthcare.

Pragmatic trials are by their current definition pragmatic in purpose (in their aim to inform healthcare decisions within routine practice) and usually pragmatic in the manner in which the intervention is modelled, but do they model the trial processes in a pragmatic way? If clinical trials could replicate the processes of routine healthcare then the results of such trials would be

more generalisable to patients in routine healthcare and thus more pragmatic. This thesis suggests that the fifth key criterion for appropriate clinical trial design from the patient's perspective is that trials aim to replicate the processes of routine healthcare wherever possible (Box 4.1).

Box 4.1   Key Criterion V

V   Aim to replicate the processes of routine healthcare

4.4   Informed Consent for trials: an examination of current practice

At this point, although a key criterion for appropriate clinical trial design has been identified, it is not clear what it would mean for trial to 'replicate the processes of routine healthcare'. In order to explore what this might mean, this section starts to explore the current information and consent processes of clinical trials from the perspective of the individual patient.

The formal procedures used to recruit patients into clinical trials in the NHS are known as Informed Consent, and are regarded as an important ethical safeguard for patients entering clinical trials by the World Medical Association's Helsinki Declaration http://www.wma.net/e/policy/b3.htm accessed 19.8.08. This section describes 'Informed Consent' - the current NHS bureaucratic procedures for informing patients about research and seeking and obtaining their consent to participate in a clinical trial; and then goes on to examine current practice and experience from the perspective of the individual patient.

4.4.1   National Research Ethics Services

Since 1986, clinical research with UK NHS patients has only been able to take place after review and approval from a Research Ethics Committee (REC). Since 2007 RECs have been provided with management support and ethical guidance from the National Research Ethics Service (http://www.nres.npsa.nhs.uk) (formerly known as COREC). The National Research Ethics Services (NRES) in turn aims to ensure that their guidance conforms with the UK, EC and International agreements and legal requirements: the UK Medicines for Human Use (Clinical Trials) regulation 2004 (http://www.opsi.gov.uk/si/si2004/20041031.htm), the European Clinical Trials Directive 2001/20/EC (http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf) and the International Conference on Harmonisation - Good Clinical Practice (http://www.ich.org).

4.4.2   Informed Consent (IC)

The term 'Informed Consent' was coined in 1957 in US case law but has its roots in the Nuremburg Code of 1947 constituted in the aftermath of Nazi war crime trials. 'Informed Consent' has become a central concern in both healthcare and recruitment to research. As mentioned earlier (4.2.1) under the current 'opt in' situation researchers cannot contact patients directly, but must only be approached by their current clinician and asked if they wish to participate.

4.4.3 Information sheets & consent forms

In order to participate, all competent patients must have read an information sheet and signed a consent form. The NRES website (http://www.nres.npsa.nhs.uk/) provides a 157 page document to guide researchers called *'Information sheets and consent forms: Guidance for researchers and reviewers' v2* May 2007. The NRES Guidance document recommends a two part information sheet (p.8-9) and a separate consent form (p.32) for patients in order to obtain Informed Consent to participate in research. The guidance about information sheets states that:

> *"Part one should provide brief and clear information on the essential elements of the study: the condition or treatment under study; the voluntary nature of involvement; what will happen during and after the trial, what treatment may be withheld; the participant's responsibilities; the potential risks, inconvenience or restrictions, benefits, and the alternative(s).*
>
> *Part two should contain additional information on factors such as confidentiality and data protection, communication with the GP, indemnity and compensation, and publication. This should be read and understood before the participant decides whether they want to participate."*
> http://www.nres.npsa.nhs.uk/docs/guidance/Info_sheet_and_consent_form_guidance.pdf accessed 16.11.07)

The NRES Guidance document does not state what consent forms must contain. Instead there is a definition of Informed Consent, a specimen consent form, and a list of 22 elements that information for participants should include, all from the ICH- GCP Guide trials of investigational medicinal products.

4.4.4   Informed Consent: definition

NRES does not offer its own definition of Informed Consent but refers to the ICH-GCP definition which defines Informed Consent as:

> "*A subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed Consent is documented by means of a written, signed and dated Informed Consent form*"

However, the ICH-GCP definition of Informed Consent does not specify which "*aspects of the trial*" are "*relevant to the subjects decision to participate*".

4.4.5   Consent form

The consent form consists of five statements that the patient must read and confirm their assent to by ticking a box.

1. *'I confirm that I have read and understand the information sheet dated….. version…. For the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily'*
2. *I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected*
3. *I understand that relevant sections of my medical notes and data collected during the study may be looked at… I give my permission for these individuals to have access to my records.*
4. *I agree to my GP being informed of my participation in the study*
5. *I agree to take part in the above study.*

The form is then signed by the patient and the person taking consent and dated.

4.4.6   Discussion

All NHS research must be approved by an NHS Research Ethics Committee (REC) and patients must only be contacted for participation in research by their clinicians and in order to participate, all competent patients must have read an information sheet and signed a consent form.

The NRES Guidance (which supports and guides RECs) invokes the authority of the international guidelines (ICH-GCP) in that NRES does not offer its own definition of Informed Consent but instead refers to the ICH-GCP definition which states that patients are informed of *"all aspects of the trial that are relevant to the subject's decision to participate ".* There is no clarification in this definition or in the ICH-GCP guidelines as to which aspects of the trials are relevant to the subject's decision to participate. But NRES stipulates that participants should be provided with information such as "*what treatment may be withheld as well as the potential risks, inconveniences, restrictions, benefits and alternatives"* but provides no rationale for this stipulation.

There is no reference made in either the NRES Informed Consent guidelines or the international ICCH – GCP guidelines as to the impact of the different types of information given, or the ethics of providing information to patients about uncertainty as to treatment allocation. Likewise, there is no reference made to the different types of consent that are sought or the conflict of motives between patients and scientists conducting research.

The literature reported that the most common barrier to patient participation in trials was patient concerns about information and consent. The next section attempts to understand the implementation of NRES Informed Consent procedures from the patient's perspective.

4.5.   Informed Consent procedures: the patient's perspective

The existing Health Services Research literature provided clarity as to the reasons why patients do not participate in clinical trials, but no solutions. So in the search for an appropriate solution the following approach was taken. Social psychology attempts to explain patterns of behaviour

in a general sense and one's psychological development in, and interaction with, a social environment. 'Social constructionism' is a popular method used in social psychology, which focuses on uncovering the ways in which individuals and groups participate in the creation of their perceived social reality. Within constructionist thought, 'social constructs' are concepts or practices that appear normal and obvious to those who accept them, but in reality are artefacts or inventions of a particular culture or society. Political scientists such as Brekke & Sirnes (2006) have suggested that Informed Consent is such a construct and that the construct of Informed Consent functions both as a 'regulatory tool' and signifier of 'normal' and responsible scientific conduct (Brekke & Sirnes, 2006). This thesis adopts the position that 'Informed Consent' is an example of a social construct, a construct which describes socially and legally acceptable ways of accessing patients and recruiting them for the purposes of research.

4.5.1   Deconstruction

Social constructionism uses the technique of deconstruction to look for suppressed and/or multiple meanings in a text (e.g. NRES Guidance) in order to expose the ideology which is implicit in this form of communication (Punch, 1998). Ideology imposes limits on what can and cannot be said and deconstruction aims to expose these limits (Punch, 1998). This section takes the NRES text: *'Information sheets and consent forms: Guidance for researchers and reviewers' v2* May 2007, viewing it as a form of communication, a type of discourse, a text/discourse written within an ideology, and attempts to 'deconstruct' this text/discourse from the patients perspective. The use of two concepts central to the NRES IC discourse 'Information' and 'Consent' is examined within this discourse. This thesis offers just one of many possible deconstructions of this complex area, a deconstruction informed by the author's personal experience of participating as a clinician in a trial (section 1.6.1-1.6.5).

4.5.2   Information

In order to obtain consent to clinical trials research, the current NRES Informed Consent discourse emphasises that consent must be informed i.e. all information in the form of written documents and verbal information is supplied to patients. Some examples of the use of the term 'informed' in the NRES guidance include: *'Informed Consent', 'after having been informed of all aspects of the trial', 'signed and dated Informed Consent form'.* The NRES text was read and multiple types of information were identified, some explicit some implicit. This thesis offers one possible typology of these multiple types of information (A-F) and discusses the possible impact each type of information may have on the individual patient and on the research. How similar or different each type of information is to the types of information present in routine healthcare is also discussed.

A. **'There is a healthcare/treatment option that may benefit you' -** This type of information is given in routine healthcare at the appropriate point for the patient – i.e. when there is the possibility that they will get it. This information raises expectations (especially for 'new'

treatments) and thus from the research viewpoint introduces the possibility of expectation bias, and disappointment/resentful demoralisation bias (Brewin & Bradley, 1989) if the preferred allocation is not given. To quote a NHS consultant: *"It is no good offering access to … care then …making people wait for weeks with no certainty about who will or won't be seen" (Health Service Journal, 2007, 'Doing well by depression' Supplement 6, p16).* Types of information B-F are peculiar to the context of research but rarely found in routine healthcare:

B. 'This is research' – this informs the patient that this is research and NOT routine healthcare. The names and authorities of those responsible for the research provides the context and credibility of the research. The legal context is given by providing information about who to complain to, and who is legally responsible, what might be described as the "entry and exit" rules of research. Information that **research** is taking place can also sometimes increase expectation of benefits – increasing the expectation bias/disappointment bias (Brewin & Bradley, 1989).

C. 'We want to observe you..' – this informs the patient that researchers want to observe them, collect data, perform tests, and implies that this data is going to be used comparatively, though this is not explicitly stated. The impact of knowing that one is being observed, data collected, tests performed can have many effects depending on the patient and the observations required. The impact of being observed has been described as the Hawthorne effect and as such is a well documented phenomenon that can affect behaviours and results in observational work (Torgerson & Torgerson, 2008).

D. 'We are not sure…' – this informs the patient as to the uncertainty about the benefits and harms of treatment. In research terms this is known as 'equipoise' or 'the uncertainty principle'. The clinician admitting that they 'do not know which the best treatment is' has an impact on both the clinician and how the patient perceives the clinician – disempowering the clinician in both the clinician's eyes and the patient's eyes[22]. Thus information about the uncertainty regarding the benefits/harms of treatment can impact negatively on the therapeutic relationship.

E. 'We are going to play a game of chance' – this informs the patient that they are going to be allocated to their treatment group randomly rather than according to either the beliefs/knowledge of their healthcare provider or their own preferences. Information about random allocation to groups means that (if the patient has a treatment preference) the patient

---

[22] One of my supervisors told me the following anecdote that they had been told by a Canadian surgeon participating in a workshop on designing clinical trials. The Canadian surgeon reported explaining a trial to a potential participant and the fact that there was uncertainty about the best treatment. At the end of the discussion the surgeon asked the patient if he had any questions. *"Yes"* said the patient, *"Can you refer me to a surgeon who **does** know what is the best treatment for me?"*

knows that they may not get the treatment they want, and the clinician may not be able to give the patient the treatment that they want (if the clinician has a treatment preference). Information as to the random allocation to groups may reinforce the clinician's uncertainty regarding the best treatment for the patient, and potentially disempowering the clinician and altering the therapeutic relationship.

Knowledge of uncertainty as to treatment allocation may bias the results through disappointment or demoralisation affecting the reporting of both patient reported and objective outcomes (Torgerson & Sibbald 1998). Uncertainty as to treatment allocation rarely occurs in routine healthcare[23] and is a significant barrier to clinical trial recruitment (Ross et al., 1999). In 1982, Appelbaum et al. coined the term the 'Therapeutic misconception'. This is the mistaken but commonly held belief of study participants that therapy and research are governed by the same primary goal: to advance the individual's patient's interests (Dresser, 2002). One example of this is the fact that patients generally find randomisation (an experimental artifice) difficult to understand and apply to their treatment or their clinician's decision making behaviour as due to the therapeutic misconception, patients generally believe or like to believe that their clinician knows best.

The following situation does not apply to pragmatic RCT design – but may be worth briefly discussing:

F. 'You may receive dummy treatment' – this informs the patient that in participating in the research they will be in a situation where there is the random possibility of dummy treatment – a placebo. Information about masked placebo may result in patients wondering if they are being deceived, and thus, when reporting outcomes, question the accuracy of their own perceptions of their health and symptoms. Patients in routine healthcare however are almost never told that they may receive a dummy treatment[24].

Table 4.3 summarise the multiple types of information given at a single point in time in NRES Informed Consent procedures, but it is clear that types of information (B – F) are rarely found in routine healthcare, particularly information that treatment will be allocated by chance (randomisation) and that information *"may be withheld"*. The research specific types of information B-F can affect patients in a variety of ways e.g. increasing expectation of benefits (B), disempowering the clinician in the patient's eyes (D), altering or sabotaging the therapeutic relationship (E & F). We can see that each 'research' type of information increases the distance between patient's experiences in clinical trials from patient's experiences in routine healthcare.

---

[23] One example of uncertainty as to treatment allocation in routine healthcare is the phenomenon of postcode 'lottery' - where the location of an address determines the treatment which is available. This is perceived as unfair and part of the rationale for the existence of NICE is to rectify the unfairness of the chance in the postcode 'lottery'.

[24] Placebos are not overtly prescribed in routine healthcare but there is a long, widespread and ongoing tradition of clinicians giving placebos – treatments that will not directly address the health needs of the patient but are given in such a way that it is implied that they will e.g. antibiotics for viral infections.

This thesis argues that from the patient's (rather than trial participant's) experience the types of information that are needed are those that are provided in routine healthcare and each type of information is required when needed rather than multiple types of information all provided at a single point in time. In routine healthcare, patients are given each piece of information when they need it and as they need it. From the patient's perspective a key criterion for appropriate clinical trial design is that information is appropriate to the patient being a patient (rather than a research participant) (Box 4.2)

Box 4.2   Key Criterion VI

VI   Have 'patient' appropriate information

4.5.3   Consent

By signing a consent form a patient is agreeing to take part in a study and the study is defined by the state of affairs and the relationships described in the information sheet. This section takes the concept 'Consent' and examines its use within the NRES Informed Consent discourse. Examples from NRES Informed Consent guidance include: *'Informed Consent', 'Consent form'*. Within the NRES Informed Consent guidance statement '*I agree to take part in the above study'* there are multiple types of implicit or explicit consent. This thesis offers one possible typology of these multiple types of consent (A-F) and discusses the possible impact it may have on patients, the possible impact the consent may have on the research, and how similar or different each type of consent is to the types of consent present in routine healthcare.

Some types of consent required by Informed Consent already exist within the routine clinician patient relationships – such as: **A. Consent to receive healthcare**. However, most consents (B- F) and relationships are only found in a research context:

B. Consent to participate in research– this includes consent to the social and legal setting of research and to the "entry and exit" rules of research – e.g. how to join and leave. This relationship is perhaps similar to that of a game player to the rules of the game.

C. Consent to be observed, have data collected, have tests - The relationship here is one of the observer to the observed, and also involves the provision of information for purposes other than one's own immediate healthcare.

Consent to participate in research and consent to be observed (B & C) are two of the types of consent that are required in observational research. Experimental research however requires other types of consent (D-E).

D. Consent to treatment outcome uncertainty - consent to enter into a state or situation of uncertainty as to which is the best treatment or the effectiveness or safety of treatment.

Table 4.3   **Informed Consent deconstructed**

	Research term	Consent	Relationship or context	Information	Impact/ possible bias
A	Patient	Be treated	Clinician/ patient relationship	'There is a treatment and it may benefit you'	Expectation of benefit – Expectation bias
B	Participant	Be a research participant	Researcher/ participant in research relationships	'There is research about..'	Amplification of effect and biases of A, C, D,E, F
C	Collect data/ perform test	Be observed	Observer/ observed relationship	'We want to observe you..'	'I am special' Hawthorne effect
D	Equipoise	Treatment outcome uncertainty	State of uncertainty.. not knowing?	'We are not sure which treatment is best….'	'They don't know which treatment is best for me..' Increases patients sense of uncertainty, disempowers clinician & alters therapeutic relationship
E	Random allocation	Have no control over allocation (allocation uncertainty)	Relationship of player to game Fate, chance	'We are going to play a game of chance'	'I might not get what I want' Disappointment bias 'My patient might not get the treatment I think is best' Refusal to recruit
F	Masked Placebo	Possibility of dummy treatment	State of uncertainty Relationship of player to game Fate, chance	'You may receive dummy treatment'	'Am I better/worse or just imagining it?' 'I feel deceived'

E. Consent to allocation uncertainty (chance) - This consent involves the patient giving up direct control (patient choice) and indirect control (nominated decision maker e.g. GP). This type of consent is similar to entering a game of chance.

F. Consent to possibility of dummy treatment - This type of consent does not usually occur in pragmatic RCT design but is worth noting nevertheless. This is consent to the uncertainty of not knowing whether one's treatment is real or dummy (placebo).

Table 4.3 summarise the consents sought in current NRES Informed Consent procedures. In routine healthcare, patients consent to situations and relationships as and when they arise, but Informed Consent for clinical trials generally requests multiple types of consent to be given at a single time point. Consents B – F do not generally occur in routine healthcare, and it is obvious that each of these types of consent may impact on the patient, particularly consents D, E & F which each introduce an element of uncertainty into the healthcare experience for the patient. As with information, from the patient's perspective, the types of consent that are appropriate are those sought/given in routine healthcare, as and when required and not multiple consents at a single point in time. From the patient's perspective a key criterion for appropriate clinical trial design is that consent is appropriate to the patient being a patient (rather than a research participant) (Box 4.3)

Box 4.3   Key Criterion VII

VII Have 'patient' appropriate consent

4.6.   Discussion: the patient experience

4.6.1   Recruitment

Recruitment and Informed Consent are often seen as immutable processes that happen *before* the trial proper begins, but it is perhaps more realistic to say that a trial begins the moment that a patient is treated differently from how they are in routine healthcare; this usually starts with recruitment. Hewison & Haines (2006) state that *"Recruitment procedures are part of the science, not an administrative add-on"*. During recruitment, information can impact on the expectations, behaviour, experiences and clinical outcomes of patients even though consent has not been given e.g. hearing that '*there is a 'new' treatment* invariably leads patients and clinicians to think that the new treatment is better in some way than existing treatments. Because of the tension between the participant's right to refuse and the motivation of the researcher to achieve a high response rate, researchers have used various ways to increase

the possibility that participants obtain direct or indirect personal benefit from participating in trials e.g. ensuring that treatment is only available within the trial[25], offering financial or material rewards, building patient's expectations about the efficacy of the intervention. These incentives or inducements could be seen as a form of coercion that impacts on the voluntary nature of research participation (Wiles et al., 2006) and as such could be viewed as unethical. Researchers (e.g. Chalmers, 1995; Torgerson & Torgerson, 2008) have stated that patients frequently fare better in trials than out, regardless of whether they receive a 'beneficial' intervention. Indeed Chalmers (1995) has cited an indirect benefit as a rationale for trial participation as *"patients receiving treatments as participants in such trials seem to fare better than apparently comparable patients receiving the same treatments outside trials";* however West et al. (2005) suggest there is no difference in clinical outcomes between patients in a clinical trial and patients receiving protocol driven care and that the benefits of improved clinical care that have previously been associated with being in a trial may be explained by the use of clear clinical protocols.

4.6.2   The ethics of NRES Informed Consent in clinical trials

Not all trial designs give full information to all patients prior to randomisation i.e. the randomised consent design (Zelen design) uses post rather than prior randomisation, although this design has been strongly criticised as unethical (Schellings et al., 2006). However, the current NRES practice of providing full information regarding all the trial procedures prior to randomisation raises a number of questions as to how ethical it is:

- To tell people about a 'possible' treatment and then tell them later that they are not going to receive it?
- To ask people to consent to a state of uncertainty with regards to which treatment they are going to receive when they could be informed after the state of uncertainty has been resolved (i.e. post randomisation)?

Truog et al. (1999) argue that the requirements for consent in clinical trials are too rigorous, and that the same level of disclosure is not required in routine practice.

It appears that the NRES Informed Consent procedures (as well as much of the literature on why patients don't participate in trials) have been written on the implicit premise that patients participate in research for altruistic reasons. If patients do participate from altruism then this supposedly validates the NRES Informed Consent 'participant' (instead of 'patient') discourse.

---

[25] In paediatric oncology most children with cancer are enrolled in research because the community of practice agreed to develop an all-encompassing research agenda in order to make progress against the disease (Kolata 1999 in King et al. 2000)

4.7. Summary

This chapter has argued that the research processes begin as soon as patients are told about the existence of the clinical trial. A small number of individuals may be motivated primarily by altruism to enter trials – to be research participants, however the majority of individuals enter clinical trials are in order to obtain the best healthcare possible – to be patients – and are motivated primarily by direct/indirect benefit.

This chapter has described how ICH-GCP states subjects should be informed of all aspects of the trial that are *"relevant to the subject's decision to participate"* , but NRES Informed Consent Guidance (section 4.4.3) operationalises 'Informed Consent' as **full** rather than *"relevant"* information – recommending the inclusion of information about the "*essential elements of the study,… what treatment may be withheld".* This means that patients are given full information about random allocation to treatment group (before randomisation) and all the different types of treatments they may be allocated to, including treatment as usual or no treatment; information which although 'full' is not relevant to patients primary status and identity as patients.

Current NRES Informed Consent procedures combine multiple information and consents, but nowhere else in healthcare are these multiple types of information provided and multiple consents sought all at a single time point. The overt uncertainty inherent in D, E & F (equipoise, random allocation and masked placebo) rarely occur in routine healthcare settings (King et al., 2000). The impact of this information creates situations different from routine healthcare. The uncertainty about treatment outcomes combined with the uncertainty about treatment allocation combined with sometimes onerous procedures in return for which the patient receives unproven treatment (or placebo) means that from the individual patient perspective, often the most rational thing to do is not to participate in the clinical trial unless the patient specifically wants the new treatment which is only available within the trial.

If researchers want patients to enter clinical trials, then from the patient's viewpoint the research design needs to replicate the processes of routine healthcare – their primary relationship. In routine healthcare, the clinician provides information about a treatment at the relevant time point only to the person who is being offered the treatment. Consent is sought also at the relevant time point from the person being offered the treatment.

This thesis argues that the information provided during recruitment and the Informed Consent process needs to be '*relevant to the subject's decision to participate'* (i.e. appropriate) rather than 'full' information. An examination of the patient perspective on clinical trial participation has identified an additional three key criteria for 'what is an appropriate clinical trial design for homeopathy in the NHS?' (Box 4.4).

Box 4.4   Key Criteria V- VII

V   Replicate the processes of routine healthcare

VI   Have 'patient' appropriate information

VII Have 'patient' appropriate consent

The next chapter examines appropriate trial design from the perspective of the discipline of science – a discipline which aims to provide knowledge that will be useful from the collective patient's perspective.

Chapter 5

The Health Services Research perspective on clinical trials

5.1   Introduction

Earlier chapters covered the perspectives of the healthcare intervention, the disease condition and the patient, as to what constitutes appropriate clinical trial design. Critical issues relating to clinical trials in these areas were discussed and seven key criteria for trial design were identified (Box 5.1).

Box 5.1   Key criteria I – VII

I	Pragmatic randomised controlled trial
II	Allow for the complexity & proper functioning of intervention
III	Have findings that can be generalised to the 'with need' population
IV	Produce short and long term outcomes
V	Aim to replicate the processes of routine healthcare
VI	Have 'patient' appropriate information
VII	Have 'patient' appropriate consent

This chapter addresses the challenge of identifying key criteria for appropriate trial design from the perspective of academics who construct, conduct and critique clinical trials – the perspective of the academic discipline of Health Services Research (HSR)[26], a "*multidisciplinary field of scientific investigation*" *(AcademyHealth, 2002).*

---

[26] The HSR perspective could also perhaps be described as the collective patient perspective, since society (patients collectively) funds universities.

5.1.1   Aims

The first aim of this chapter is to identify key criteria for appropriate RCT design by exploring the current HSR perspective.

The second aim is to examine possible solutions to the methodological issues identified through an exploration of the current HSR perspective from the broader HSR perspective of all the key criteria identified from all four perspectives: the intervention, the condition, the patient and the science of HSR (I – XII).

5.2. The HSR perspective

5.2.1   Randomised Controlled Trials

The Randomised Controlled Trial (RCT) is a key HSR method and is one of the simplest and most powerful tools of research. The RCT is in essence a study in which people are allocated at random to receive one of several interventions i.e. each subject in the study has the same chance of being allocated to any particular group with randomisation normally done by reference to a series of randomly generated numbers (Torgerson & Torgerson, 2008). The logic is that if an appropriate random system is used, the likelihood is that the two groups created will be similar in respect of any particular variable.

5.2.2   Internal & external validity

The validity of the causal inferences drawn from scientific studies such as the RCT can be divided into two types– internal validity and external validity. 'Internal validity' can be defined as - the observed state of affairs *within* the study is free from bias and confounding. 'External validity' can be defined as - the observed state of affairs within the study *applies outside* the study and the results are therefore externally generalisable. RCTs are constructed to have high internal validity (by avoiding allocation and selection bias) and there are checklists to assess the internal validity of clinical trials (Jadad et al., 1996). Awareness of internal validity issues is widespread and is now addressed through many journals requiring trial reports to use the CONsolidated Standards of Reporting Trials (CONSORT) reporting guidelines (www.consort-statement.org); these guidelines include a checklist of items to include when reporting a randomised trial and includes 'flow of participants through each stage' and 'number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. These items enable the reader to directly assess the internal validity of the trial.

Internal validity is a prerequisite for external validity as the results of a flawed trial are invalid and the question of its external validity becomes irrelevant.

Due to its perceived inherent strong internal validity, the (well conducted) RCT is widely perceived as the gold standard research design for evaluating effectiveness, and systematic

reviews and meta-analyses of RCTs are regarded as the top of the evidence base hierarchy (Sackett et al., 2000a).

Despite the strong internal validity of the RCT as a research method, the lack of consideration of external validity is the most frequent criticism of RCTs and systematic reviews by clinicians (Rothwell, 2005). CONSORT guidelines state that external validity is a matter of judgement and depends on the characteristics of the participants included in the trial, the trial setting, the treatment regimens and the outcomes assessed and that '*there is no external validity per se; the term is meaningful only with regard to clearly specified conditions that were not directly examined in the trial'* (www.consort-statement.org). The concern among clinicians that external validity is often overlooked, (particularly for some pharmaceutical industry trials) is one explanation for the widespread under use in routine practice of treatments that have been shown to be effective in trials[27]. Reporting of the determinants of external validity in trial protocols or trial publications is often poor and there are no commonly used requirements for external validity that are required by funding agencies, ethics committees, medical journals or governmental regulators. Thus from an HSR perspective a key criterion of appropriate trial design needs to be that trials have both internal and external validity (Box 5.2) particularly for pragmatic trials which aim to inform healthcare decisions within routine practice.

Box 5.2   Key Criterion VIII

VIII External as well as internal validity

The external validity of trial design is not just an important issue from an HSR perspective. The external validity of RCT design has been identified as a critical issue in all three areas so far explored in this thesis: reviews of systematic reviews of homeopathy (chapter 2), reviews of interventions for hot flushes (chapter 3), and the patient perspective (chapter 4).

5.2.3   **External validity and the HTA methodology programme**

Unlike internal validity, there is no well known or commonly used method or set of tools or checklist[28] for assessing the external validity of RCTs. In order to understand the relationship between appropriate trial design and external validity more thoroughly, and to identify further

---

[27] Another explanation is that clinicians know that treatments have variable effectiveness depending on the characteristics of the patients, thus they ask 'do the results of this trial apply to this patient?' How to design studies to help clinicians treat individual patients rather than populations of patients is an important question that has not been addressed in this thesis. However, this issue is addressed in homeopathy. Homeopathy has always assessed the effect of every homeopathic remedy on individual patients using Human Pathogenetic Trials (HTPs) (also known as homeopathic 'provings'). The aim of HPTs is to identify those patient characteristics which will predispose those patients to respond well to particular homeopathic medicines e.g. patients who report feeling hot, hungry and itchy respond better to the homeopathic remedy 'sulphur' than those who do not report feeling hot, hungry and itchy. HTPs have been conducted for several thousand homeopathic medicines and are still being conducted today worldwide.

[28] There are two published checklists for external validity briefly discussed in chapter 9 (Rothwell, 2005; Downs, 1998)

key criteria for appropriate trial design, a review of the methodological issues which affect the external validity of RCTs was required. The HSR literature on the external validity of RCTs is vast, so this thesis examined a rigorous, up to date body of writing which covers this area, the NHS R&D Health Technology Assessment (HTA) programme; this provides the most appropriate body of high quality literature on trials and trial methods that relate to the purposes of NHS clinical research methods. The HTA programme was set up in 1993 following the publication of the first NHS R&D strategy, which aimed to create a research system that provided high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. The majority of HTA trials are pragmatic NHS based RCTs which aim to produce information about outcomes that have high external and internal validity. Within the broader HTA programme there is a specific HTA 'Methodology' programme which specifically aims to identify and answer important methodological questions relevant to HTA, however other areas of the HTA programme also cover methodological questions. Since this chapter is from the current HSR perspective then the literature of the NHS R&D Health Technology Assessment (HTA) programme provides an appropriate body of high quality literature on trials and trial methods that relate to the purposes of NHS clinical research methods.

5.3   Review of the HTA literature on the external validity of RCTs

5.3.1   Review aim

This review has two aims. The first aim of this review is to identify and understand the nature of the methodological issues relating to the external validity of RCTs by searching and assessing HTA reports relating to RCT design, in order to derive key criteria for appropriate trial design from the HSR perspective. The second aim of this review is to examine possible solutions to the methodological issues from the current HSR perspective, by assessing the ability of each 'possible solution' to meet all twelve key criteria for appropriate trial design.

5.3.2   Review methods

To identify and understand the nature of the methodological issues relating to the external validity of RCTs, a search of the HTA database of reports http://www.hta.nhsweb.nhs.uk/ was conducted on 2.10.07; and 396 published or commissioned/ongoing reports were identified. These comprised: NICE Technology Assessment Reports, Primary research (e.g. trials), Secondary research (e.g. systematic reviews), Methodology reports and Other reports. The HTA 'Methodology' programme aims to identify and answer important methodological questions relevant to HTA. In order to identify the core methodology issues, a search was conducted for those reports that were classified as either 'Methodology' reports or had the term 'methodology' in their title.

109 'methodology' reports were identified and their titles read.

Those reports not directly related to external validity were excluded. These included reviews of specific interventions, qualitative research, outcome measures, systematic reviews and systematic reviews of methods, health economics, public/consumer participation, action research, statistical modelling, guidelines and risk factors. The following terms were used as a guide to inclusion: trial, RCT, random$, equipoise, preferences, recruitment, ethics, and uncertainty. But as this list was not exhaustive, and this search was exploratory, the executive summaries of the reports remaining after the exclusion criteria had been applied were read in order to see if they related to the methods and issues of primary experimental clinical research.

Sixteen published reports on RCT design were identified: Ashcroft et al.,1997; Britton et al.,1998; Bartlett et al. 2005; Crow et al. 1999; Crow et al. 2002; Deeks et al, 2003: Edwards et al., 1998; King et al., 2005; Lewsey et al., 2000; MacLehose et al., 2000; Mowatt et al., 1997; Prescott et al., 1999;, Raftery et al., 2005; Robinson et al., 2005; Sutton et al., 1998; Williams et al., 2003) and one final report submitted to the NCCRM (Campbell, M., 2007) which was on the HTA website. These 17 reports were published between 1997 and 2007 and covered a wide range of issues: heterogeneity, lack of comparability between trials, recruitment, placebo, uncertainty, informed consent, clinician & patient preferences, barriers to participation, randomised vs non randomised studies, use of routine data.

Each of the 17 reports appeared to relate either directly or indirectly to recruitment issues e.g. barriers to clinicians and patients being recruited to trials, issues with the informed consent process prior to recruitment, recruiting trial populations being dissimilar to the 'with need' or 'treatment seeking' population. In presenting the results of the review, the results are reported according to the following three categories (as reports tended to focus on one aspect of recruitment issues):

- Description & implications of recruitment issues
- Analysis of the reasons for the recruitment issues
- Discussion and/or testing of possible solutions to recruitment issues.

5.3.3   Description & implications of recruitment issues

Failure to recruit and unrepresentative study populations were the two main recruitment issues described.

A. Failure to recruit: All 17 reports mention the fact that many trials fail to recruit sufficient numbers. Of 114 multi centre MRC & HTA funded trials which ran between 1994 and 2003, less than a third recruited their original target within the time originally specified, and a third had extensions in attempts to recruit the required number of participants (Campbell M., 2007). Failure to recruit has implications for both the cost, and the validity/reliability/comparability of the

results of the RCT. Recruiting sufficient numbers is thus an important key criterion for valid RCT design from the current HSR perspective (Box 5.3).

Box 5.3   Key Criterion IX

IX Recruit sufficient numbers

B. Unrepresentative study population

All 17 reports stated that many trials fail to recruit trial populations that are representative of the reference population with the trial populations often having a different clinical, demographic and psycho-social profile to the eligible treatment population as a whole. Participants recruited to trials tend to be younger, more likely to be male, white/Caucasian and healthier than the potential pool of patients from which they are recruited (Bartlett et al., 2005) and older, female, ethnic, patients with multiple co-morbidities tend to be excluded. The exclusion from trials of those people who are likely to be in need of an intervention can result in disparities between the reference population and the 'trials' population, thus compromising trial generalisability. For example an analysis of 27 trials of statins for use for secondary prevention of coronary heart disease (CHD) revealed that those aged 65+ formed nearly two thirds of the 'with need' population but only one fifth of the trial populations (Bartlett et al., 2005).

Measures of absolute effectiveness are vital for the analyses of benefit, harm and cost effectiveness. If the different population groups are not adequately represented and effectiveness is variable, then such analyses may be severely biased or skewed. Study populations should be representative of all patients currently being treated for the condition (Bartlett et al., 2005; Britton et al., 1998). In the USA appropriate representation of women and ethnic minorities in publicly funded trials is required by legislation. However in the UK inclusivity in research is not currently formally promoted. Thus from an HSR perspective a key criterion for appropriate clinical trial design is that the recruited population is representative of the reference population (Box 5.4)

Box 5.4   Key Criterion X

X Recruited population is representative of the reference population

5.3.4   Reasons for recruitment issues

Half the reports discussed the reasons for recruitment issues (Campbell M, 2007; Prescott et al., 1999; MacLehose et al., 2000; Britton et al., 1998; MacLehose et al., 2000; Robinson et al., 2005; Ashcroft et al., 1997; Edwards et al, 1998). There was widespread acknowledgment that the reasons for the failure to recruit and the lack of representativeness of those recruited were

complex and discussions concerning the reasons for recruitment issues fell into two overlapping areas – A. Preferences and B. Informed consent.

A. Preferences

Patient and clinician treatment preferences were acknowledged as a barrier to recruitment (Campbell M., 2007; Prescott et al., 1999; MacLehose et al., 2000; Britton et al., 1998). MacLehose et al. described an example of the impact of preferences in the CASS (1984) study. This study accrued a prospective registry of 2,099 patients with coronary artery disease of which only 780 (37.2%) consented to randomisation. There was some discussion as to whether practitioner and patient preferences influenced the outcome of treatment and thus caused the results to be misleading (Britton et al., 1998; MacLehose et al., 2000) with opinion on whether this was the case being split. The way in which preferences were seen to act as a barrier was that if the trial design meant that the fulfilment of any patient and practitioner preferences might be thwarted, then the practitioner or patient was much more likely to either refuse to consent to participate or drop out if they did not receive their preferred treatment option.

One essential criterion for the authorisation for randomisation of trial participants is that there is equipoise between the treatment options. This is also known as the uncertainty principle. Equipoise can be also described as 'equal preferences between the treatment options'. Equipoise (equal preferences) in the scientific/medical community however does not necessarily imply equipoise (equal preferences) with regards to treatment options in either individual practitioners or patients. There are currently no bureaucratic procedures to assess or check whether individual clinicians are in equipoise regarding treatments before a trial begins, but a few trials now attempt to measure the preferences of patients prior to randomisation to groups (Torgerson & Torgerson, 2008).

If a trial design leaves patients and clinician preferences unaltered then these preferences will not act a barrier to patient and clinician trial participation. Thus from an HSR perspective a key criterion for an appropriate pragmatic clinical trial design is that patient and practitioner preferences are unaltered (Box 5.5)

Box 5.5   Key Criterion XI

XI   Patient and practitioner preferences remain unaltered

B. Informed consent

Two broad areas were discussed in relation to Informed Consent – understanding the information and the ethics of randomisation and uncertainty.

Understanding the information

Many reports identified a range of issues regarding Informed Consent (Prescott et al., 1999; Robinson et al., 2005; Ashcroft et al., 1997; Edwards et al., 1998; MacLehose et al., 2000). Many patients do not fully understand the information given to them during consent consultations (Ashcroft et al., 1997); in particular most patients do not understand the meaning or implications of certain key abstract concepts (equipoise, randomisation), integral to giving consent to participate in an RCT (Ashcroft et al., 1997; Edwards et al., 1998; Prescott et al., 1999; Robinson et al., 2005). Many people participating in research are unaware of the differences between participating in a research study and receiving routine treatment in the clinical setting. Most lay patients believe that doctors in RCTs DO know best, and transfer their expectation that their doctor will act in their (the patient's) best interest from a clinical setting to a research setting – this is known as the *'therapeutic misconception'*.

Additionally, most patients believe that it is unacceptable to use chance to decide upon what treatment they will receive (Robinson et al., 2005) and many patients are unwilling to be randomised (MacLehose et al., 2000). Ashcroft et al., (1997) suggests that many RCTs run the risk of being unethical in practice, even if they seem to be ethical in principle due to patients being unable to understand the principles and purposes of the RCT.

Thus from an HSR perspective a key criterion for appropriate clinical trial design is that the procedures of Informed Consent are not a barrier to recruitment (Box 5.6).

Box 5.6   Key Criterion XII

XII Informed Consent procedures are not a barrier to recruitment

The ethics of randomisation and uncertainty

The ethics of randomisation, the impact of uncertainty and the disparity between the assumptions underlying trial design and the assumptions about trial design in the publics understanding were highlighted in several reports (Edwards et al., 1998; Ashcroft et al., 1997). Edwards et al., describes uncertainty as 'an underpinning issue' of the ethical arguments which bear on RCTs and discusses both the Kantian and the Utilitarian perspectives on the ethics of participation in RCTs, concluding that fully informed consent for all patients is an unobtainable ideal.

What is seen as 'equipoise' from the researcher's perspective is seen as 'uncertainty' from the patient's perspective. The existence of equipoise justifies the use of randomisation in the research design, however providing information as to 'randomisation' (and hence 'equipoise'/'uncertainty') acts a barrier to participation and brings ethical issues to bear.

5.3.5   Identifying key criteria

The aims of this methods review were to identify and understand the nature of the methodological issues relating to the external validity of RCTs by searching and assessing the

literature of the HTA literature, and to derive key criteria for appropriate trial design from the HSR perspective.

This review of the HTA literature identified five key methodological issues for the external validity of RCTs, explored the reasons for these issues and derived five key criteria for appropriate trial design Key Criteria VIII – XII (Box 5.7).

Box 5.7   Key Criteria VIII - XII

An appropriate trial design should:
VIII External as well as internal validity
IX   Recruit sufficient numbers
X   Recruited population is representative of the reference population
XI   Patient and practitioner preferences remain unaltered
XII Informed Consent procedures are not a barrier to recruitment

5.4   Possible solutions to methodological issues

Having identified both the key methodological issues from the HSR perspective, and the five key criteria for appropriate clinical trial design from the HSR perspective, it is now time to address the second aim of this review – to examine possible solutions to the methodological issues. This examination will be conducted using not just those key criteria derived from the current HSR perspective (VIII – XII) but will incorporate a broader HSR perspective by using all 12 key criteria from all four domains: the intervention, the condition, the patient and the science of HSR (I – XII). This section assesses the ability of each 'possible solution' to meet all 12 key criteria from this broader perspective.

HTA reports which discussed possible solutions to RCT recruitment issues fell into two types; firstly, those that discussed using data from non randomised studies instead of RCTs, and secondly, those that discussed using alternative RCT designs.
Six HTA reports examined ways of circumventing recruitment issues to RCTs by asking whether either routine clinical data or non randomised study data could be used instead of data from RCTs. Four reports (Raftery et al., 2005; Bartlett et al., 2005; Lewsey et al., 2000; Williams et al., 2003) looked at clinical databases that collect routine data and two published reports (Britton et al., 1998; MacLehose et al., 2000) looked at data from non randomised studies[29].

---

[29] Non randomised studies – also sometimes described as quasi-experimental and observational studies (QEO)

5.4.1 Database and non randomised studies

Routine clinical databases were seen as containing potentially cheaper and more representative information than that obtained by RCTs (Williams et al., 2003). In all, 270 UK routine databases identifying either health states or healthcare interventions were assessed as being of relevance (Raftery et al., 2005) and development of a 'register of registries and databases' was recommended (Bartlett et al., 2005). Problems in uniformity in data collection and in identifying, accessing and extracting the relevant information of routine database information were discussed (Williams et al., 2003). Closer policy links between routine data collection and Research & Development, and investment in the more promising databases were recommended (Raftery et al., 2005) as well as classifying the research data needed for HTA and mapping these data to potential routine sources (Williams et al., 2003).

A commonly held belief is that non randomised studies produce larger effect sizes than randomised studies. However all three HTA reports which examined this belief concluded that RCTs did not systematically produce effect sizes either greater or lesser than non randomised study designs (MacLehose et al., 2000; Britton et al., 1998; Deeks et al., 2003) although they rarely gave the same estimates as RCTs. These reports concluded that RCTs should remain the preferred study design for evaluating health technologies due to their inherently good internal validity, but high quality non randomised study designs should be considered when RCTs are impracticable (MacLehose et al., 2000).

The next question to ask is how well do data from databases and non randomised studies meet the twelve key criteria for appropriate clinical trial design from the four perspectives? Each criterion has been abbreviated wherever possible and summarised in Box 5.8 below.

I   Pragmatic randomised controlled trial

II   Allows the complexity & proper functioning of intervention

III Findings generalisable to 'with need' population

IV Produce short and long term outcomes

V   Aim to replicate the processes of routine healthcare

VI 'Patient' appropriate information

VII 'Patient' appropriate consent

VIII External as well as internal validity

IX Recruit sufficient numbers

X   Recruited population is representative of the reference population

XI Patient and practitioner preferences remain unaltered

XII Informed consent procedures are not a barrier to recruitment

population), XI (Patient and practitioner preferences unaltered), IV (Produce short and long term outcomes) and XII (Informed consent procedures are not a barrier). However, studies which use data from routine clinical databases or non randomised study data lack randomised data and thus are vulnerable to the possibility of confounding by unknown prognostic factors, and thus have poor internal validity and thus key criterion VIII (External as well as internal validity) is not met.

5.4.2   Alternative RCT designs

Researchers have proposed and used a variety of designs to overcome a range of problems with RCTs and there is a vast literature reporting these designs. A review of this literature is outside the scope of this thesis; however there is an HTA report[30] (MacLehose et al., 2000) which identified ten study designs that have been proposed to address one or more of the problems often found with standard RCTs. The rest of this chapter examines these 10 RCT designs in more detail. All ten designs (as well as the standard pragmatic RCT design) are reported in Table 5.1. This table describes the rationale (advantages) and disadvantages of each design, and states which key criteria are met by the design.

The HTA report (MacLehose et al., 2000) classified designs as either 'hybrids' if they intended to provide both RCT and non randomised estimates of effectiveness, or 'RCT variants' if they adhered to the principle of randomisation but included some modifications.

Hybrid designs

These study designs collect data from both randomised and non randomised patients. Each hybrid design has been created to address one or more of the problems that arise from seeking consent to randomisation prior to randomisation: patients reluctance to consent to random allocation, lack of clinician equipoise with regards to treatment for individual patients, patient preferences for certain treatments. Each of these four hybrid designs includes an observational arm or arms consisting of those patients who (or whose clinicians) do not consent to them being randomly allocated, as well as several arms which have patients randomly allocated to them. Each of the hybrid designs results in two sets of data – data from those who are randomly allocated and data from those who are not randomly allocated.

The Comprehensive cohort study design

The first hybrid design is the Comprehensive cohort study design (described by Francis, 1954; Olschewski, 1985; Olschewski, 1992; in MacLehose et al., 2000) which was created to address the issue of patients having a preference against giving consent to random allocation to treatment. This design starts with a cohort of patients who are then asked to consent to randomisation; all patients are followed up, irrespective of whether or not they consented to andomisation. At the end of the study there are two sets of data - observational data from those

---

[30] This report aimed to investigate the association between methodological quality and the magnitude of estimates of effectiveness derived from RCTs and quasi-experimental and observational studies (QEOs).

who did not consent to randomisation and experimental data from those who did consent to randomisation. This is a pragmatic RCT design (I), which allows the complexity & proper functioning of the intervention (II), enables the production of long term outcomes (IV), where patient & practitioner preferences are unaltered (XII) and where informed consent is not a barrier (XII). However this design does not replicate the processes of routine healthcare because some of the patients are asked to consent to random allocation to treatment prior to randomisation. This design also does not increase the number of patients recruited to the randomised arm(s).

Patient preference trial

The second Hybrid design is the Patient preference trial (Brewin & Bradley, 1989) which was created to address the issue of patient preferences for certain treatments over other treatments. This design allows patients with strong preferences to choose their preferred treatment rather than be randomly allocated to treatment. This design differs from the Comprehensive cohort study design in that patient's preferences are elicited and their stated preferences then determines which group each patient is allocated to, whereas group allocation in the Comprehensive cohort study design is determined by the patients preference for/against random allocation to treatment. It is interesting to note that the trial design is called 'Patient preference trial' rather than a 'Participant preference trial', thus acknowledging the importance of treating individuals in trials primarily as 'patients' rather than 'research participants'.

This is a pragmatic randomised controlled trial design (I) which allows the complexity & proper functioning of the intervention (II) where patient preferences are unaltered (XI). However this design has no advantages over the current problematic standard pragmatic RCT design as it does not increase the number of patients recruited to the randomised arm(s).

Table 5.1   Standard pragmatic and alternative RCT designs

	Trial design	Rationale for the design	Key Criteria fully met	Disadvantages of the design
	Standard pragmatic RCT (randomisation post consent)	To obtain measures of effectiveness from a trial design with high internal validity	I, II	Poor recruitment rates, patient and clinician treatment experiences altered, poor generalisability, lack of long term outcomes, unrepresentative recruited population, poor external validity, ethical issues and informed consent a barrier to recruitment
Hybrid designs	**Comprehensive cohort study design**	Addresses the issue of patient preferences against consent to random allocation to treatment	I, II, IV, XI, XII	Does not increase the number of patients recruited to the randomised arm(s)
	Patient preference trial	Allows patients with strong preferences to choose between treatments offered	I, II,	Does not increase the number of patients recruited to the randomised arm(s)
	Two stage trial	To separate the physiological from the psychological effects of treatment	I, II	Does not increase the number of patients recruited to the randomised arm(s)
	Clinician preferred trial	Allows clinicians with preferences to choose between treatments for their patients	I, II	Does not increase the number of patients recruited to the randomised arm(s)
RCT variants	**Randomised play-the-winner**	To increase the number of patients receiving the superior treatment during the trial	II	Quasi randomisation therefore poor internal validity
	Randomised discontinuation trial	To minimise the number of patients exposed to placebo	None	Withdrawal of treatment from treatment responders increase drop out and presents ethical issues Uses placebo – therefore not a pragmatic RCT design
	Change to open label	Offers patients the possibility of unmasked treatment within the trial	None	Proxy outcome – time until patient requests open label Uses placebo – therefore not a pragmatic RCT design
	Placebo run-in trial	Increased efficiency by weaning out non compliers in first phase	None	Uses placebo – therefore not a pragmatic RCT design
	Double randomised consent design	To address issue of obtaining informed consent prior to randomisation	I, II, III, (V,VI,VII), VIII, IX, X, XI, XII	If TAU then patients told they have been randomly allocated to no treatment Ethical issues Statistical analysis issues
	Single randomised consent design	To address issue of obtaining informed consent prior to randomisation	I, II, III, V, VI, VII, VIII, IX, X, XI, XII	Ethical issues Statistical analysis issues

Two stage trial

The third hybrid design is the Two stage trial which was designed to separate and quantify the physiological effects of a treatment from the psychological or placebo effects of treatment. Eligible patients are randomised into one of two study arms: 'option' or 'random'. In the 'option' arm, patients are offered a free choice between treatments being evaluated, but if they have no preference then they are asked to consent to be randomised to one of the treatments. In the 'random' arm patients are asked to consent to be randomised to either treatment. The 'option' arm collects randomised and non randomised data and the 'random' arm collects randomised data only. There are obvious difficulties; explaining this trial design to patients, recruiting patients with preferences to this design, and analysing the results from of the six arms. There have been no published trials that have used this design. This is a pragmatic trial design (I). However this design does not increase the number of patients recruited to the randomised arm(s) and thus has no advantages over the current problematic standard pragmatic RCT design.

Clinician preferred treatment trial

The fourth hybrid design is the 'Clinician preferred treatment trial' design. This design allows clinicians with pre-existing treatment preferences for patients to influence the probability of that patient receiving that treatment (via panel discussions). Thus allocation to treatment is determined by clinicians for some patients and by chance for those patients where clinicians do not have pre-existing treatment preferences. This design overcomes the ethical difficulties for clinicians who want to participate in an RCT but who are not in equipoise for all patients who satisfy the eligibility criteria. This is a pragmatic RCT design (I) which allows the complexity & proper functioning of the intervention (II) and would probably enhance the number of patients recruited (IX). However, this design like all the hybrid designs does not increase the number of patients recruited to the randomised arm(s) and thus has no advantages over the current problematic standard pragmatic RCT design.

All four hybrid designs seek to address problems of standard trial design. Compared to the standard RCT design, the proportion of patients recruited may be increased in each of the designs, however, none of these hybrid designs help increase the proportion of people recruited to the **randomised** arms. Thus despite any advantages these designs may bring with regards to external validity these hybrid designs have no advantage over the standard RCT design with regards to internal validity.

5.4.3   RCT variants

There are six 'RCT variants' (Randomised play-the-winner design, Randomised discontinuation trial, Change to open label, Placebo run-in trial, Single randomised consent design and Double randomised consent design). Each RCT variant seeks to overcome one or more problems with the standard RCT.

Randomised play-the-winner design

The first RCT variant is the 'Randomised play-the-winner design'. This is a response adaptive design which places new patients on the treatment arm that appears at the time to have better outcomes, thus swiftly estimating the benefits (or lack) of a treatment. This design seeks to anticipate the result of the trial before the end of the trial (and thus result in more patients receiving the more effective treatment than the less effective treatment during the trial). A success with a patient receiving treatment A leads to the next patient receiving the same treatment. A treatment failure would mean the next patient is allocated to treatment B. This design perhaps mimics the way clinicians 'try out' treatments in their patients in routine clinical practice. This design has rarely been used (lack of use however is not justification for dismissing this or any design), and there is controversy over how to determine appropriate allocation probabilities. This design uses quasi randomisation as each patient's treatment is determined by the success or failure of one of the treatments on the previous patient rather than randomly allocated. This means that this design has poor internal validity. So regardless of any enhancement to its external validity the design is of little use as an RCT design.

Randomised discontinuation trial

The second RCT variant is the 'Randomised discontinuation trial' which is a two phase trial design. The rationale for this design is to attempt to assess the clinical activity of a drug while minimising the number of patients exposed to placebo treatment. Phase I is an open phase in which all patients are given the treatment. At the end of Phase I, the effects of the treatment are reviewed and recruited patients are divided into 'responders' and 'non responders'. 'Non responders' includes patients who suffer adverse health effects, non compliers and non improvers. Non-responders are excluded from Phase II of the trial in which responders are randomised into placebo and verum groups. This design decreases the heterogeneity of the randomly assigned population, resulting in increased statistical power with smaller patient numbers.

This is a non pragmatic RCT design which has been rarely used. The drop out rate of those responders who initially responded to treatment and are then randomised to placebo is likely to be high as it is unlikely that patients who are responding to treatment would then consent to the possibility of being randomly allocated to placebo. This design is unlikely to receive NHS ethical approval as it means that clinicians have to withdraw treatment from patients who appear to have benefited if they are randomised into the placebo group. The randomised discontinuation trial does not appear to facilitate any of the key criteria for appropriate trial design.

Change to open label design

The third RCT variant is the Change to open label design. This is a placebo RCT design which begins in the conventional manner but allows patients to change to open (as opposed to masked) treatment when they want to. The outcome measure is the time until a patient requests

open treatment, analysed using survival methods. There is no published report of an evaluation using this design. It is unclear how well knowledge of 'time until patient request open treatment' can serve as a proxy marker for 'patient satisfaction with their progress' and thus can inform clinical decision making. As the design uses placebo it is not a pragmatic RCT design and therefore does not meet key criterion I or facilitate any of the other key criteria.

Placebo run-in trial

The fourth RCT variant is the commonly used **'**Placebo run-in trial' two phase design. Non compliers are weeded out during the first 'placebo' run in phase, thus increasing the efficiency of the second 'randomised' phase. This design aims to provide measures of efficacy in 'compliers'. Thus the value of the information derived in informing decisions about providing treatment is limited. The 'Placebo run-in trial' design is the same as the standard RCT but with the additional preliminary placebo run-in phase. This design does not facilitate any of the key criteria for appropriate trial design. Both the 'Change to open label' and the 'Placebo run-in trial' designs have placebo as an integral part of their design and thus are not pragmatic RCT designs.

Randomised Consent Designs

The fifth and sixth RCT variants are both Randomised Consent Designs - the **Double Randomised Consent Design (DRCD)** and the **Single Randomised Consent Design (SRCD).** Both designs seek to address issues around obtaining informed consent prior to randomisation. The randomised consent design was originally proposed by Marvin Zelen, as a way of maximising recruitment by only seeking consent to participate from those already randomised to the intervention arm, thus helping overcome the discomfort for physician and patient of explaining equipoise and acknowledging uncertainty (Zelen, 1979). It was hoped that the design would maximise external validity and statistical power while maintaining an acceptable level of internal validity. The DRCD and SRCD (known collectively as 'Randomised Consent Designs[31]) randomises patients *prior* to seeking consent to participate in the trial. The two types of randomised consent design are distinguished according to the extent to which participants are informed about treatment options.

Double randomised consent design (DRCD)

The DRCD method randomises patients, tells all patients of their random allocation *post* randomisation, and then asks for their consent to take part in the study. Patients who refuse the treatment to which they have been randomised can receive the alternative treatment. This means that in a pragmatic RCT of TAU vs TAU + new treatment, patients are told that they have been randomly allocated to TAU & not the new treatment - information which does not happen in routine healthcare. Information as to random allocation to TAU does not replicate the

---

[31] The randomised consent design is also known as the: 'randomisation prior to consent' design, 'post-randomised consent design', 'Zelen's design' and 'pre consent design'

processes of routine healthcare and thus compromises key criteria from the patient's perspective - key criteria V, VI & VII.

Single randomised consent design (SRCD)

The SRCD seeks consent to trial participation only from those allocated to a non standard treatment arm. Those allocated to the control treatment (usual care or no treatment) are not asked to give their consent to participate in the trial. The SRCD is a pragmatic design which meets all the key criteria derived from the patient's perspective: randomisation before consent enables the information given to patients to be appropriate to their role as patients (VI), likewise with consent (VII) and thus the processes of routine healthcare are replicated (V) more closely than either the DRCD or the standard RCT design which uses randomisation post consent. The SRCD can enable all four key criteria from the HSR perspective to be met: the design can help recruit sufficient numbers (IX), recruit a population that is representative of the 'with need' population (X), enable patient and practitioner preferences to remain unaltered by the design (XI) and thus there is the possibility that Informed Consent procedures will not be a barrier to recruitment (XII). Although the SRCD does not directly fulfill key criterion IV (Produce short and long term outcomes) this design has the potential to meet 11/12 of the key criteria for appropriate clinical trial design and thus has the potential for greater external validity than either the DRCD or the standard pragmatic RCT design or any of the other hybrid or variant RCT designs.

However, despite the obvious strong potential external and internal validity of the SRCD, there is controversy over the use of Randomised Consent Designs generally. The ethical and methodological issues of using Randomised Consent Designs are described and discussed in the next section with a view to deciding whether the SRCD is feasible or not.

5.4.5   Ethical and methodological issues with Randomised Consent Designs

In the last decade there has been much discussion of the ethical and methodological issues of Randomised Consent Designs, designs which do not seek consent to randomisation. This discussion has sometimes been opaque due to the blanket use of the term 'Informed Consent' and a lack of differentiation as to the type of information/consent being discussed (Dawson, 2004). Two recently published systematic reviews of Randomised Consent Designs (Schellings et al., 2006; Adamson et al., 2005) have identified trials which use the design.

Adamson et al. (2005) identified 58 healthcare trials published between 1990 and 2005 using this method, the majority (45/58) of which used the single randomised consent design (SRCD). Most used the randomised consent design to avoid biases associated with patients knowing about alternative treatment (e.g. Hawthorne effects, resentful demoralisation, avoidance of contamination) rather than as an aid to participant participation (Torgerson & Torgerson, 2008). Most trials experienced some crossover from one group to the other (mean = 13.8%, IQR 2.6%

- 15%), although this was usually reported as being 'within acceptable[32] limits'. An ITT analysis was used in 74% of trials. Schellings et al. (2006) identified 50 trials using the randomised consent design with 23/50 trials using the single randomised consent design (SRCD). Of the 29 trials which gave reasons for using the randomised consent design, 16/29 used the method to prevent contamination, and 11/29 used the method to avoid problems with randomisation such as simper IC procedure, simpler participant recruitment, and avoiding unnecessary distress and confusion for patients. Non compliance in those trials that used the SRCD reported a median of 15% (IQR 7% - 39%) in the treatment offer group compared to a median of 0% (IQR 0-4%) in the no treatment offer group[33]. Reported median loss to follow-up in the SRCD trials was 9% for the treatment offer group and 0% for the no treatment offer group.

5.4.6   Ethical arguments

The ethical issues of standard Informed Consent procedures used in RCTs have already been discussed in section 4.6.2 (from the patient's perspective) and 5.3.4 B (from the current HSR perspective). This section summarises the arguments found in the literature on the ethical issues of Randomised Consent Designs (Zelen, 1990; Allmark, 1999; Homer, 2002; Altman et al., 1995; Adamson et al., 2006).

It is argued that in certain situations the randomised consent design is more ethical than standard consent procedures; Allmark et al. (1999) argue for the design to be used in situations where the process of obtaining consent for randomisation has the potential to harm the subject (e.g. some neonatal trials) and Homer (2002) argues for its use in order to avoid disappointment of the conventional pre consent randomisation designs. These authors argue that the **ethical advantages** of the randomised consent design are that:

- o patients do not need to understand or contemplate the difficult concept of randomisation
- o it avoids creating additional anxiety (re. randomisation) at times of acute illness
- o patients do not have to have their confidence in the clinicians undermined by thinking they don't know what to do
- o it avoids raising expectations that they may access a new treatment only to find their hopes dashed if allocated to the control group (resentful demoralisation)

Allmark et al. (1999), Homer (2002), Anon (1984) argue that the **ethical disadvantages** of using the randomised consent design are that the randomised consent design results in the:

- o denial of information to patients regarding all possible trial options prior to randomisation
- o denial of patient choice regarding whether randomised to treatment options
- o overselling advocated treatment

and thus the design is unethical in most or all circumstances.

---

[32] The term 'acceptable' here presumably equates to avoiding a Type II error (concluding there is no difference when there is) in the context of an ITT analysis
[33] Schellings describes these as the 'index' and 'reference' groups

The patient's opinion on the ethics of single Randomised Consent Designs was one of the themes explored in qualitative research by Snowdon et al. (1999). This study reported the results of open question interviews with 44 parents of 25 babies who had participated in a trial that used a single randomised consent design (SRCD). The opinions of some reflected a belief in a general right to information, whereas others were firmly grounded in personal experience. A total of 20 parents were for the SRCD and 21 against. Interestingly, and perhaps predictably[34], those parents whose babies were randomised to the standard treatment were more likely to be anti SRCD (12 vs 8) and those parents whose babies were randomised to the new treatment were more likely to be pro the SRCD (16 vs 5).

5.4.7 Individual-cluster RCTs

There are strong parallels of the randomised consent design with another type of trial design – the individual-cluster RCT (Torgerson & Torgerson, 2008). In cluster RCTs, clusters of people rather than individuals are randomised. The two widely used arguments for randomisation by cluster are: (1) the intervention may be administered to and affect entire clusters of people as opposed to individuals and (2) although the intervention is given to individuals it may also affect others within that cluster (contamination or herd effect of vaccination). Edwards et al., (1999) have described the ethical issues in the design and conduct of cluster RCTs. In cluster RCTs informed consent for trial entry (randomisation pre consent) cannot be obtained individually, so the decision whether a particular cluster participates in the trial is taken by a 'guardian' who has the power to deliver that cluster e.g. Chief Executive of a PCT , hospital or school (as well as an Ethics committee). The guardian must act in the best interests of the cluster. There are two types of cluster RCTs: cluster-cluster trials and individual-cluster trials. In cluster-cluster RCTs a guardian must consent/ decline both trial entry and the intervention as a single package, but in the case of individual-cluster RCTs it is only trial entry (randomisation pre consent) that takes place without individual consent, as the individual treatments can be declined or accepted by each individual participant and they choose to continue with routine care.

5.4.8 Methodological issues of Randomised Consent Designs

The methodological advantages and disadvantages of the design have been discussed widely in the HSR literature (Zelen, 1979; Zelen, 1990; Altman et al., 1995; Schellings et al., 1999; Torgerson & Roland, 1998; Homer, 2002; Dawson, 2004; Boter et al., 2004; Campbell et al., 2005; Schellings et al., 2006). Homer (2002), Dawson (2004) and Boter et al., (2004) argue for the randomised consent design in situations where requiring prior consent would lead to potentially biased results i.e. to avoid disappointment bias and subjective bias in the recruitment process (Homer, 2002). Torgerson & Torgerson (2008) argue for the design to be used in situations where it is important to estimate the effects on a whole population such as evaluating population based interventions e.g. bone density screening. Schellings et al. (1999) argue that

---

[34] If it is assumed that patients (and parents of patients) participate in research primarily in order to gain direct and/or indirect benefit.

the design may be the best choice for heroin-provision experiment in order to avoid massive drop out or non-compliance in the control group and Schellings et al. (2006) argue for a limited use of Randomised Consent Designs where: (1) Blinding is deemed necessary, but is impossible to achieve by sham procedures (placebo) and (2) The experimental treatment seems attractive to potential participants.

These authors argue that the **methodological advantages** of the randomised consent design are that the design can:

- o   Enable treatment discussion with the patient that is more straight forward & closer to 'routine' clinical practice
- o   Avoid patient withdrawal/ non-compliance when randomised to TAU
- o   Avoid disappointment/resentful demoralisation bias
- o   Evaluate the effect on a whole population of a population based intervention

The main **methodological disadvantage** of the randomised consent design is the effect of the design on:

- o   'Cross over' rates & ITT analysis

The main disadvantage is if patients refuse their allocated treatment and thus effectively 'cross over' into the opposing group. This cross over will dilute any treatment effect and make it harder to observe a difference using an ITT analysis, thus possibly causing a Type II error (concluding there is no difference when there is). Cross over does occur in standard RCT designs but the likelihood of crossover will be greater in a randomised consent design because the majority of participants who may refuse treatment are not screened out before randomisation. The larger the cross over the larger the sample sizes needed to cope with dilution effects, which can increase the cost of the trial. The review of the design in cancer treatment trials (Altman et al., 1995) concluded that it was hard to justify the use of the design in cancer trials due to 'crossover' problems.

5.5   Summary

This chapter asked the question: 'What is an appropriate trial design from the current HSR perspective?' It described the importance of internal validity in trial design in order to facilitate the drawing of strong causal inferences (Key Criterion VIII: Internal and external validity). In order to identify important issues with regards to both internal and external validity, a broad and high quality body of literature within HSR – methodology reports of the NHS R&D HTA programme - was reviewed. Critical methodological problems for the external validity of rigorous pragmatic clinical research in the NHS were identified (recruitment numbers, recruitment representativeness, patient and clinician preferences, and informed consent) and a further four key criteria for appropriate trial design were derived from the HSR perspective IX (Recruit

sufficient numbers), X (Recruited population is representative), XI (Patient and practitioner preferences unaltered), and XII (Informed consent procedure is not a barrier).

This chapter sought to identify the most appropriate RCT design to use to assess the clinical and cost effectiveness of treatment by a homeopath for women with menopausal hot flushes to fit all twelve key criteria. There is nothing specifically unique about 'treatment by a homeopath' compared to any other type of treatment involving a clinician e.g. surgery, psychotherapy, GP treatment/healthcare etc. Thus whatever is an appropriate method for assessing the clinical and cost effectiveness of treatment by a homeopath is also likely to be an appropriate method for assessing the clinical and cost effectiveness of any intervention delivered by a clinician, and may indeed be an appropriate method for assessing the clinical and cost effectiveness of any healthcare intervention regardless of the extent to which the clinician is involved in the delivery of the intervention.

In the search for an appropriate RCT design to use to assess clinical and cost effectiveness which fits all twelve key criteria, ten clinical trial designs were examined (four hybrid designs & six 'RCT variant' designs), none of which met all twelve criteria (Table 5.1). None of the hybrid designs helped increase the proportion of patients recruited to the randomised arms in comparison to the standard RCT method although the Comprehensive cohort study design did enable the production of short and long term outcomes. Of the RCT variants, the randomised play-the-winner is a quasi randomised design, and the three other designs (randomised discontinuation trial, change to open label design, placebo run-in trial) all used placebo and therefore are not pragmatic designs. However the single randomised consent design is a pragmatic trial design which does not produce short and long term outcomes (IV) but which appears to help increase the proportion of patients recruited in comparison to the standard RCT method and may enable 11/12 of the key criteria (I, II, III, V, VI, VII, VIII, IX, X, XI, XII) to be met.

The next chapter offers an RCT design that attempts to meet all twelve key criteria using elements of two existing RCT designs: the single randomised consent design and the Comprehensive cohort study design

Chapter 6

The 'Patient Cohort' RCT design

6.1   Introduction

6.1.1   The viewpoints of four stakeholders

This thesis addresses the question: *"What type of clinical trial design can provide the information needed to make decisions about the provision of homeopathy in a publicly funded healthcare system?"* The first approach to this question involved the identification of four perspectives on clinical trial design (the intervention, the clinician, the patient and the science of Health Services Research) with the purpose of identifying key criteria for clinical trial design. Twelve key criteria for appropriate clinical trial design were derived (Diagram 6.1) through critical analysis and reviews of the literature from these four viewpoints. It is important to note that these key criteria have been derived by the PI using secondary research and have not been corroborated by primary research with representatives of the four perspectives.

6.1.2   A preliminary answer

Thus, taking account of these key criteria, a preliminary answer to the question addressed by this thesis is: *The type of clinical trial design which can provide the information needed to make decisions about the NHS provision of homeopathy is a pragmatic randomised controlled trial, that allows the intervention to function properly for patients (and clinicians), whose results are generalisable to patients 'with need', which produces short and long term outcomes for patients, where patients experiences and preferences are the same as in routine healthcare, where information and consent occur as they would do in routine healthcare for patients, where*

patients in the trial are representative of the 'with need' population of patients, yet has both external and internal validity (and thus can establish causality with some degree of certainty).

6.1.3 Twelve overlapping key criteria

Diagram 6.1 depicts all twelve key criteria for clinical trial design from each of the four perspectives: the intervention, the clinician, the patient and the science of HSR. Eleven of the key criteria relate to external validity issues and the twelfth (Key Criteria VIII) relates to both 'Internal and external validity'. It is clear that many of the key criteria overlap either fully or partially, for example 'Findings generalisable to 'with need' population' (III) and 'Recruited population is representative' (X). This overlapping is a result of the multiple perspectives from which these key criteria have been derived and could be viewed as a form of triangulation or corroboration of the importance of each criteria.

Diagram 6.1 **Twelve key criteria for appropriate trial design**
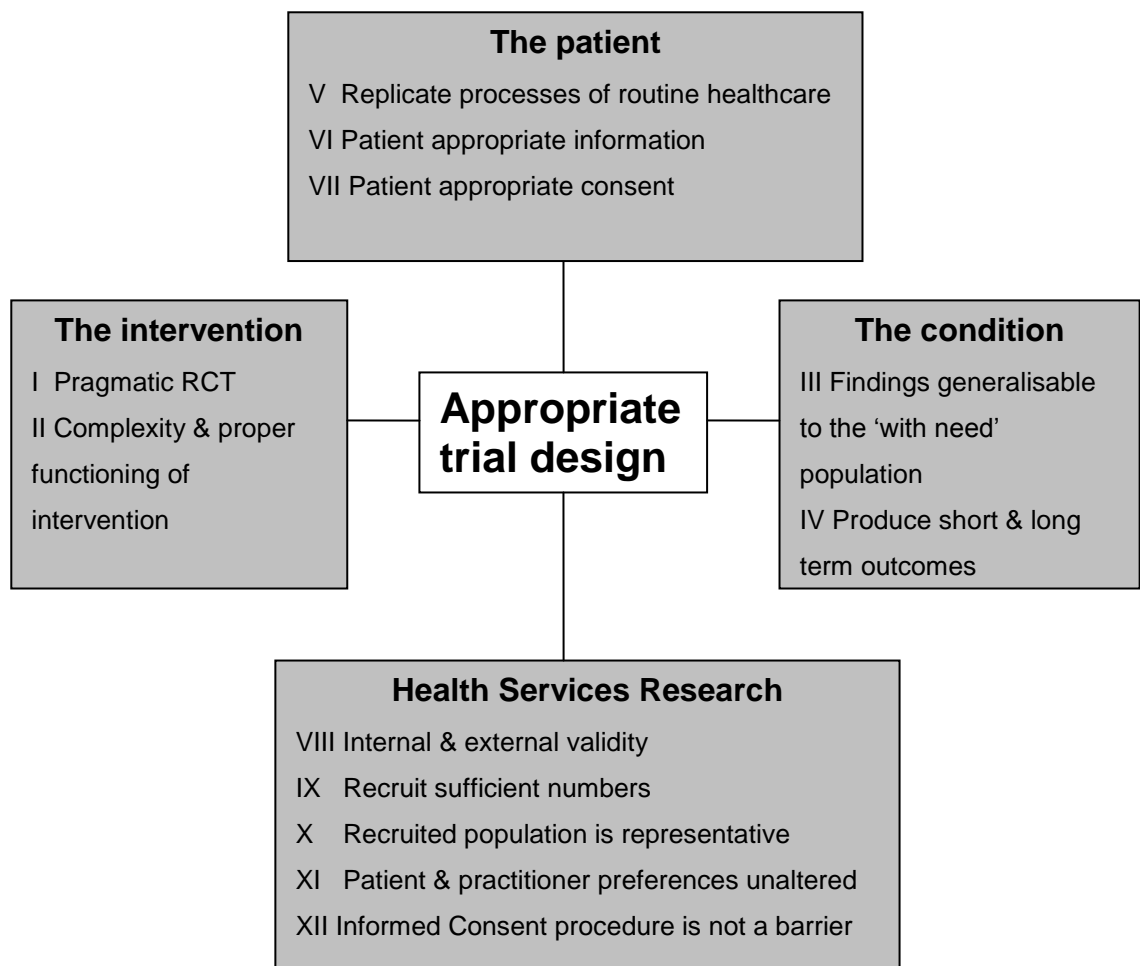
6.1.4 Aims & objectives

The aim of this chapter is to fully describe the 'Patient Cohort' RCT design. The objectives of this chapter are to:

- Define the 'Patient Cohort' RCT design
- Illustrate the application of the 'Patient Cohort' RCT design to a healthcare question
- Describe key features of the design
- Discuss how far the 'Patient Cohort' RCT design meets the 12 key criteria for appropriate clinical trial design
- Compare the design with standard, alternative and hybrid clinical RCT designs.

6.2 The 'Patient Cohort' RCT design

6.2.1 Defining the 'Patient Cohort' RCT design

The Patient Cohort RCT design aims to enhance the external validity and efficiency while retaining the internal validity of the RCT. The design offers a solution to some of the issues relating to recruitment, informed consent and randomisation as they pertain to the 'needs and preferences of individual patients'. Box 6.1 offers a definition of the 'Patient Cohort' RCT design.

Box 6.1   The 'Patient Cohort' RCT design

The 'Patient Cohort' RCT design consists of an observational Cohort of patients with the condition of interest within which multiple RCTs are embedded.

- **For each RCT, eligible patients are identified, a proportion of whom are then randomly selected to be offered the intervention.**
- **The outcomes of the selected eligible patients are compared to the outcomes of the non-randomly selected eligible patients.**
- **Patient information and consent replicate the processes of routine healthcare wherever possible.**

6.2.2 Patient centred NHS

The 'Patient Cohort' RCT design describes a collection of methods. Throughout the various stages (design, scientific review, NHS ethical review & governance, MHRA approval, the pilot), several different names were used (and considered) to describe this collection of methods. Some examples are 'Observational sampling Trial', 'Split consent RCT', 'Randomised Cohort Controlled Trial', 'Patient centred RCT', 'Modified Zelen trial', each name emphasising one particular feature or set of features of the design. The cohort is an essential part of the design and therefore one name that was considered was the 'Cohort RCT', however, that did not fully capture the essence of the design. The 'Patient' component of the name arose during the writing up period and was incorporated as it reflected the importance of the patient perspective

6.3   An illustration: Obesity research

In order to illustrate the 'Patient Cohort' RCT design, the design is applied to obesity research. Obesity is a common clinical condition which has big implications for future UK health and NHS healthcare resources. It is predicted that there will be many trials funded and conducted in this condition over the next decade.

6.3.1   Researching obesity using the 'Patient Cohort' RCT design
The Patient Cohort

A sample Cohort[35] from the 'with need' population, the patient group to be investigated is identified e.g. Obese patients with a Body Mass Index (BMI) of ≥ 30[36]. Prospective Cohort members are informed that the research is taking place and of the need to obtain information and recruit patients to form an 'Obesity Cohort'. Two consents are sought: consent to provide data and consent for that data to be used comparatively. Those patients with a BMI ≥ 30 who consent, then become patients in the Obesity Cohort, and are periodically asked to provide outcomes (e.g. weight, waist measurement, medication, quality of life, comorbidities, visits to GP etc.) at appropriate time intervals (e.g. quarterly). This design is depicted in Diagram 6.2. As observation is inexpensive relative to treatment, and recruitment rates to observational studies are generally high, large numbers of patients can be recruited to the Obesity Cohort.

Identifying patients eligible for Tx A

Sufficient information needs to be collected from the Cohort in order to be able to identify those patients who meet the inclusion/exclusion criteria for any particular trial. When an intervention for obesity (e.g. treatment 'A') reaches equipoise, all members of the Obesity Cohort who are eligible for Tx A (i.e. meet the inclusion/exclusion criteria for treatment (Tx) A) are identified – these are described as N(A).

---

[35] This cohort could be identified either purposively or by consulting existing large routine databases such as the General Practice Research Database (http://www.gprd.com/home/) of anonymised longitudinal medical records from primary care with over 3.4 million active patients from over 450 primary care practices
[36] The characteristics of the 'with need' population define the inclusion criteria for the Cohort

Random selection to the intervention/ trial of Tx A

A proportion of the eligible population (N(A)) are then *randomly selected* to the intervention (the Offer of Tx A) – in Diagram 6.2 this group is described as n(A). Those patients randomly selected from the eligible group N(A) to the offer of the intervention group - n(A) - are then given information about the treatment, about treatment uncertainty, about the fact that they have been selected at random. Their consent to treatment is then sought. Those that give consent to treatment are then treated.

Assessing the effects of Tx A

To assess the effectiveness of the offer of Tx A, the periodical outcomes provided by the entire Cohort are used. No special outcomes are measured for those offered the intervention. For an intention to treat analysis (ITT) to assess the effectiveness of the offer of treatment, the outcomes of n(A) are compared to the outcomes of N(A) – n(A). This process can be repeated for Tx B to form N(B) and n (B) etc. Tx B, C, D etc can be trialled within the Obesity Cohort either at the same time or at a later date. The trial design also enables indirect comparisons between Tx A, B, C and D since each has been compared against the same Treatment As Usual (TAU) Cohort.

Diagram 6.2   The 'Patient Cohort' RCT design
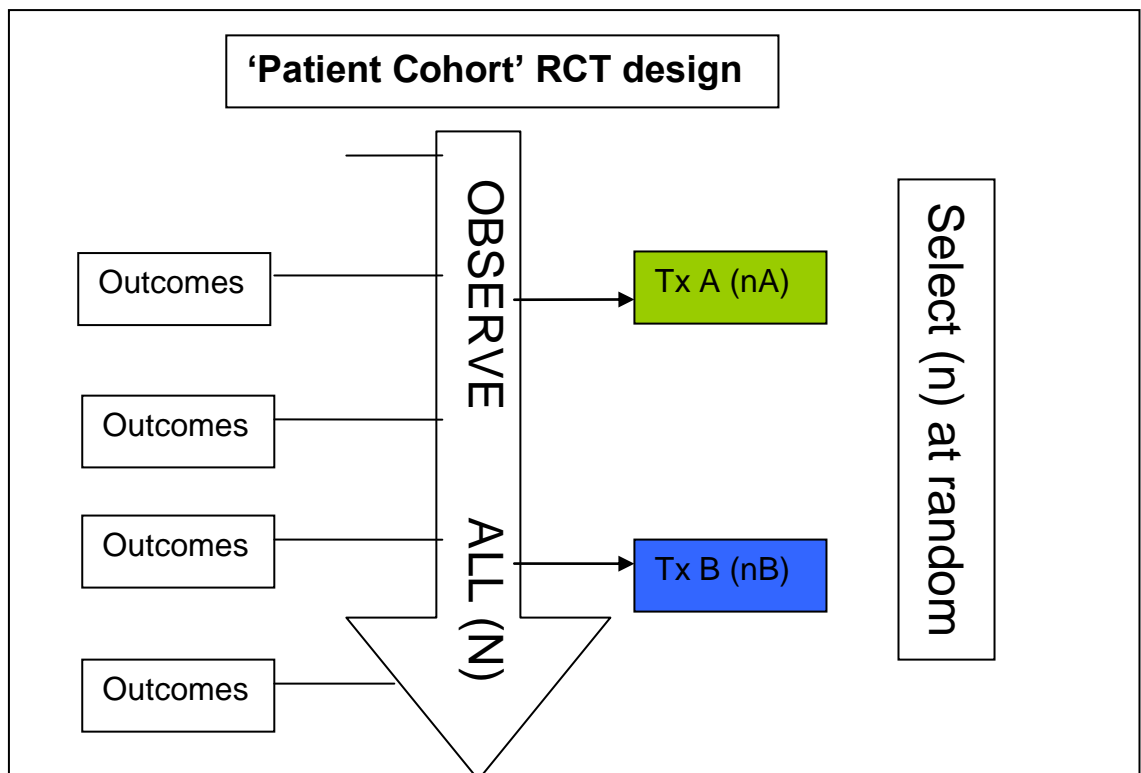
6.4 Main features of the design: the Cohort

There are three main features of the 'Patient Cohort' RCT design: The Cohort, Random Selection, and Patient centred informed consent. These are described in sections 6.4.- 6.6 and listed in Diagram 6.6. How each feature relates to the twelve key criteria is examined and possible advantages and disadvantages of each feature in comparison to standard pragmatic RCT design are discussed.

6.4.1 Definition

The first essential feature of the 'Patient Cohort RCT' is the 'Cohort'. A 'Cohort' consist of a group of people who share a common characteristic of interest within a defined period e.g. BMI ≥30 as of January 2009, who are surveyed or observed at regular intervals (Crombie & Davies, 1996).

6.4.2 Advantages of the Cohort

The 'Cohort' feature provides a number of research benefits: scoping information e.g. the natural history of the disease and any associated factors, information on TAU, long term outcomes, facility for multiple trials, uncontaminated control group, increased comparability of research, strengthened statistical inferences & generalisability.

6.4.3 Scoping information

The Cohort provides scoping[37] information that can be used for designing trials. Experimental research needs to be based on up to date observational data as to the normal progression of disease, factors which may influence the course or outcome of the disease, clinicians prescribing patterns, patterns of behaviour by patients, comorbidities etc., however, in many diseases the natural history is not well characterised. Often there is a time lag between changes in the behaviour of populations, and information about these changes being published in the public domain e.g. news of the change in HRT prescribing habits and attitudes to HRT after the publication of the WHI trial data took several years to be published in peer reviewed journals (Ness, 2005). Locating trials within an observational Cohort can provide up to date relevant information and accurate estimates of the public health benefit of any intervention can be gained by gathering data on rates of compliance.

6.4.4 Treatment as usual (TAU)

The Cohort feature embeds the research within existing routine healthcare practice (TAU) and thus allows constant comparison to TAU with any intervention trialled. Indirect comparisons also mean that interventions can be compared with each other as well as TAU. Information

---

[37] [37] The MeSH definition of scoping is: *"a means of identifying issues and concerns, their significance and the range of alternatives"* (http://cancerweb.ncl.ac.uk/cgi-bin/omd?scoping).

from the Cohort can provide the routine, accurate and systematic information that is needed to inform clinical practice and health services management.

Standard pragmatic trials with a TAU arm often have to stipulate what exactly TAU comprises of, often many months before the trial takes place, thus TAU is often artificial. In contrast, in the 'Patient Cohort' RCT design, those patients in the Cohort (who are not in the Offer group) are not contaminated with information about any of the trial treatments as they are only observed. Thus TAU in the Patient Cohort RCT design really is TAU.

6.4.5   Long term outcomes

There is a general concern in medicine regarding the longer term effects of interventions (Crombie & Davies, 1996). However, clinical trials have generally been conceived in what could be called an 'SAS' style – a problem is identified and a research team leaps in to test an intervention (that has reached societal equipoise), recruits trial participants, randomly allocates to groups, measures outcomes and then leaves. When a different intervention reaches equipoise, then a different research team leaps in – recruits trial participants, randomly allocates to groups, measures outcomes and then leaves. This 'SAS' style of trial often produces short term outcomes of a variety of different interventions with heterogeneity of trial populations and outcomes. The collection of long term outcomes can also enable the measurement of infrequent adverse events (like condition registers), the assessment of interventions designed to prevent rare events, and the evaluation of outcomes which occur far in the future. The Cohort feature of the 'Patient Cohort RCT' thus enables both short and long term outcomes to be produced (Key Criterion II).

6.4.6   Facility for multiple trials

The Cohort is used repeatedly to test each intervention as it reaches equipoise – the Cohort thus becomes a facility for multiple trials (Diagram 6.2). The core range of outcome measures used throughout the duration of the Cohort will enable comparison not just between an intervention and TAU but indirect comparison between interventions A, B, C etc as well. The current situation is that many competing interventions have not been compared so sometimes indirect comparisons are made in which two interventions are compared through their relative effect versus a common comparator, however, this indirect comparison sometimes results in a significant discrepancy (Song et al. 2003). The Cohort facility for multiple trials will enable more reliable indirect comparisons than is currently possible with multiple 'SAS' style of trial.

6.4.7   Increased comparability, statistical power & efficiency

The CASS study (1984) reported in section 5.5.2 demonstrated that recruiting patients to be observed is significantly easier than recruiting patients to be randomly allocated to treatment groups. Because recruitment of patients in standard RCTs is difficult (and expensive) standard RCTs usually randomise patients on a 1:1 basis as this gives the greatest statistical power for the least number of patients. However, for the 'Patient Cohort' RCT design, recruitment of patients to the observational Cohort will be easier (and thus cheaper) than recruitment to

standard RCTs, thus random selection could be on a unequal basis e.g. 3:1 (i.e. 3 controls: 1 intervention). In order to adequately power any given RCT, it would be possible to have more patients in the control group but less patients in the intervention group than when using 1:1 (equal) randomisation. As well as reducing trial treatment costs, the increased efficiency of the 'Patient Cohort' RCT design will result in fewer patients being offered experimental interventions with uncertain outcomes.

6.4.8 Disadvantages & limitations

There are four possible disadvantages to the use of Cohort feature in the 'Patient Cohort RCT' design as compared to the standard RCT: attrition, acceptance rate, cost and TAU & masking/blinding.

6.4.9 Attrition

Cohorts are susceptible to attrition (where participants are lost during the study and cannot be included in the analysis) as members of the Cohort recover from their condition (and hence are no longer eligible), move away (mobility attrition), die, or lose interest in the research (compliance attrition, research fatigue attrition). Attrition can reduce the statistical power of the inferences as well as introduce bias when those who drop out of the Cohort differ from those who continue. The Cohort will need continuous replenishment in order to have sufficient numbers of patients with the condition, and consideration will need to be given to incentives to motivate members of the Cohort to continue providing information. However, attrition in the Cohort should be less than attrition in a standard RCT design where patients are asked to comply with being in a situation with uncertainty regarding treatment allocation, and possible disappointment at not being allocated the preferred treatment as well as being observed[38].

6.4.10 Acceptance rates

In a standard RCT design only those who are happy to receive the intervention(s) are recruited and thus included in the trial population. In the 'Patient Cohort' RCT all those patients who meet the inclusion criteria become members of the eligible population for the trial, but the likelihood or not of them accepting the intervention(s) is unknown. If the number of patients who accept the intervention is significantly smaller than the number who are offered the intervention, then this has implications for any 'Intention To Treat' analysis of the results,. This issue is discussed further in chapters 9 and 10.

6.4.11 Cost

The financial cost of the Cohort will depend on the size of the Cohort, the cost of recruiting patients to the Cohort, the cost of obtaining data from the Cohort, the number of elements in the data collection and the attrition rate. The more trials that use any one Cohort then the

---

[38] Reducing attrition by weaning out non compliers with the intervention or data collection is an issue that has been addressed by the preliminary run in phase of the placebo run-in trial design (section 5.5.8).

cheaper each trial will be and the more cost effective it will be to maintain the Cohort. The size of the Cohort needs to be consistent with the plan for its exploitation. Cost should be less than multiple independent 'SAS' style trials but may not be so.

6.4.12 TAU & masking/blinding

The 'Patient Cohort' RCT is primarily a pragmatic trial design and as such is designed to test interventions against TAU. If patients/practitioners need to be masked as to treatment allocation or interventions are tested against other pre-specified interventions e.g. Orlistat vs Rimonabont (two obesity treatments) rather than TAU, then although there is a ready made Cohort of patients to recruit from, some of the advantages of the design will be lost: increased comparability of research, strengthened statistical inferences, replication of processes of routine healthcare, and patient appropriate information and consent (Key Criteria VI & VII).

6.5   Main features of the design: random selection

6.5.1   Random allocation of all vs random selection of some

The second feature of the 'Patient Cohort RCT' design is the way in which 'randomisation' is conceptualised and operationalised. The aim of randomisation in experimental research is to generate two or more groups whose selection and treatment have not been influenced or determined by anyone or anything other than chance (e.g. the investigators, the clinicians, the study participants, date of birth, date of recruitment) and where all known or unknown prognostic factors are distributed at baseline purely by chance. This thesis argues that the generation of two (or more) groups whose membership is a result of chance can be done equally well by either <u>random allocation of all</u> or <u>random selection of some</u>. Random allocation of all patients (N) into two groups nA and nB in terms of end result is the same as randomly selecting from N into nA as it is solely due chance whether any patient is or is not selected into nA. For the purposes of an RCT random selection from N into nA provides two groups where all known or unknown prognostic factors are distributed at baseline purely by chance: nA and (N – nA).

6.5.2   Definition of random selection

The 'Patient Cohort RCT' has operationalised randomisation as *random selection of some (n).* This contrasts with randomisation in the standard RCT which is operationalised as *random allocation of all (N).* If randomisation is conceptualised as *random selection of some (n)* patients from the observational Cohort*,* then it can be argued that neither information about randomisation, nor consent to be randomised, is relevant to the patient's status until after they

have been randomly selected to a non TAU group. Only those patients who have been selected at random are told post hoc that this is how they have been selected for treatment A. The two methods – random allocation of all (N) and random selection of some (n) are depicted side by side in Diagram 6.3.

The 'Patient Cohort' RCT design is a form of Single Randomised Consent Design (SRCD) (which has been discussed in chapter 5) where no information regarding randomisation or possible treatments is given prior to randomisation and only those patients allocated to the non TAU group receive information about randomisation post randomisation.

### 6.5.2   Patient status – in a trial or not?

A lay person's idea of 'being in a trial' is likely to involve trying out a new treatment, not receiving the usual one (Allmark, 1999). But in standard pragmatic trials all patients who are recruited are 'in the trial' even if they are randomised to TAU. Patients participating in research that uses the 'Patient Cohort' RCT design can be seen to have several different types of status:

1. In an observational Cohort
2. Eligible for an intervention (the 'with need' population)
3. Randomly selected to be offered the treatment

6.5.3   Advantages

The main advantage of using *random selection of some* rather than *random allocation of all* is that it enables the trial processes to more closely mirror the processes of routine healthcare.

Diagram 6.3   **'Random selection of some' versus 'Random allocation of all'**
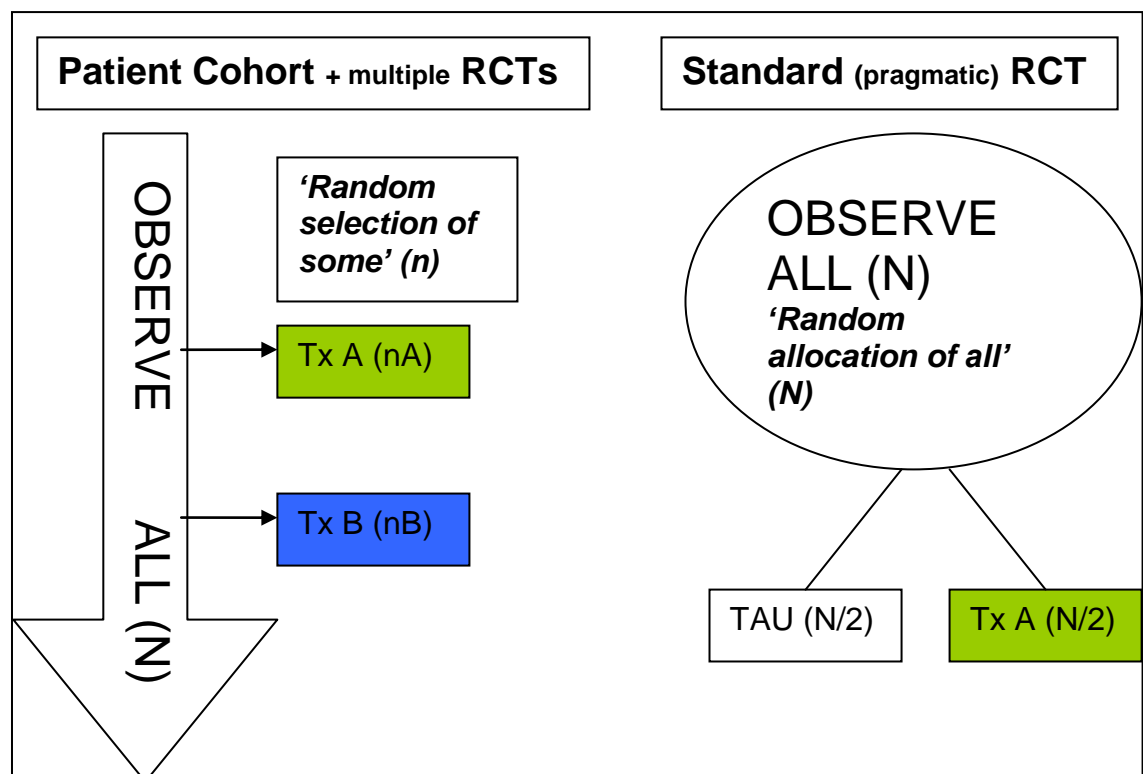
Patients in routine healthcare are rarely told that their treatment is going to be decided by chance (and even when their clinician is unsure as to which treatment is best, their clinician will often mask their uncertainty from the patient). *Random selection* enables the patient to be given information about randomisation **after** selection to be offered the treatment rather than the standard RCT method of giving information about random allocation to groups/treatments, **before** random allocation to the treatment or control group. The operationalisation of randomisation as *random selection* thus means that the patient receives information that is appropriate to their role as patient (Key Criterion VI) and the patient gives consents that are appropriate to their role as a patient (Key Criterion VII). Although this way of operationalising randomisation is closer to routine healthcare, patients randomly selected to the Offer group still need to be told that they have been randomly selected – an event that does not generally happen in routine healthcare.

6.5.4   Congruence with motives

It has been already identified (section 4.5.2) that the majority of patients believe that doctors **do** know best regarding their treatment whatever the setting (the 'therapeutic misconception') (Appelbaum et al., 1982; Dresser, 2000), and that the majority of patients either don't understand random allocation or find it unacceptable as a means for deciding treatment. Chapter 4 identified that the majority of patients primarily participate in research because of an expectation of personal direct or indirect benefit from participation. Given these facts, it does not make sense to ask doctors to inform/consent patients to random allocation if it is at all avoidable. Patients are patients, not game players and clinicians are clinicians, not researchers – asking either to participate in a 'game' situation of random allocation will result in 'game experiences of healthcare rather than experiences of routine healthcare. Random selection of some rather than random allocation removes the need to 'play the game' and thus enables both clinicians and patient's experiences to be nearer to routine healthcare experiences. Random selection goes some way towards satisfying Key Criterion V (Replicate processes of routine healthcare).

6.6   Main features of the design: 'Patient centred informed consent'

The third feature of the Patient Cohort RCT is described as 'Patient centred informed consent'. 'Patient centred informed consent' is perhaps better described as a 'collection of methods' rather than a single 'feature'. Chapter 4 described the current standard approach to Informed Consent, with its multiple information and consents all given and sought at a single time point to all patients regardless of what treatment they would ultimately receive (or not receive). Chapters 4 & 5 identified several critical issues associated with the current standard approach

to Informed Consent: the patient's lack of understanding of random/ chance allocation to treatments, the clinician's and patient's aversion to uncertainty in the healthcare setting, the fact that Informed Consent often appears to act as a barrier to recruitment. The impact of these critical issues on patient recruitment appeared to suggest that there is a need for a different approach to informed consent. 'Patient centred informed consent' offers a different approach and a possible solution to these issues.

6.6.1   Definition

The aim of 'Patient centred informed consent' is to minimise the impact of the scientific uncertainty on the patient and the clinician. The standard informed consent procedures are split up so that instead of all possible information being given and all possible consents sought all at a single time point prior to randomisation, information and consents, wherever possible, are 'split up' so that the manner in which they occur replicates the processes of routine healthcare. The features of 'Patient centred informed consent' are as follows:

- consent to observation is sought **prior** to random selection
- treatment information is provided **post** random selection and only to those randomly selected for non TAU
- consent to treatment is sought **post** random selection only from those patients selected for non TAU
- no treatment information is provided about treatments that patients **might** or **might not** receive
- consent to random selection is not sought **prior** to random selection
- those not randomly selected to treatment are not informed that they have **not** been randomly selected to treatment

Diagram 6.4 depicts the delivery of the different types of information and consent within the 'Patient Cohort' RCT design for an 'Intention To Treat' analysis.

6.6.2   Advantages

'Patient centred Informed Consent' reduces the operational burden of Informed consent procedures for both patients and clinicians. The splitting of the different types of information given to the patient and the different types of consent sought from the patient enables several the research to replicate processes of routine healthcare (Key Criterion V), the information to be appropriate for the patient (VI) and the consent to be appropriate for the patient (VI).

6.6.3   Patient appropriate information

'Patient centred informed consent' enables the information flow to mimic that which exists in routine healthcare – patients are observed and **when** a treatment becomes available and is deemed that it might be beneficial for the patient **then** they are given information about the treatment and asked to consider consenting to the treatment. By replicating the processes of routine healthcare uncertainty for the patient is kept to a minimum. 'Patient centred informed consent' increases the clarity and certainty for the patient about the research thus enabling the

fulfilment of Key Criterion V (Replicate processes of routine healthcare), and Key Criterion VI (patient appropriate information).

6.6.4   Patient appropriate relationships & consent

Similarly, 'Patient centred informed consent' enables the relationships and concomitant consents to be more similar to that which occurs in routine healthcare. The different types of consents and their implied relationships are kept separate i.e. the observer/observed relationship is separated out from the receive healthcare/deliver healthcare relationship. Thus making it easier for the individual patient to understand what is being asked of him. The better the comprehension of a situation, the easier it is to make a decision about whether to consent to it.

Diagram 6.4   **'Patient centred informed consent'**
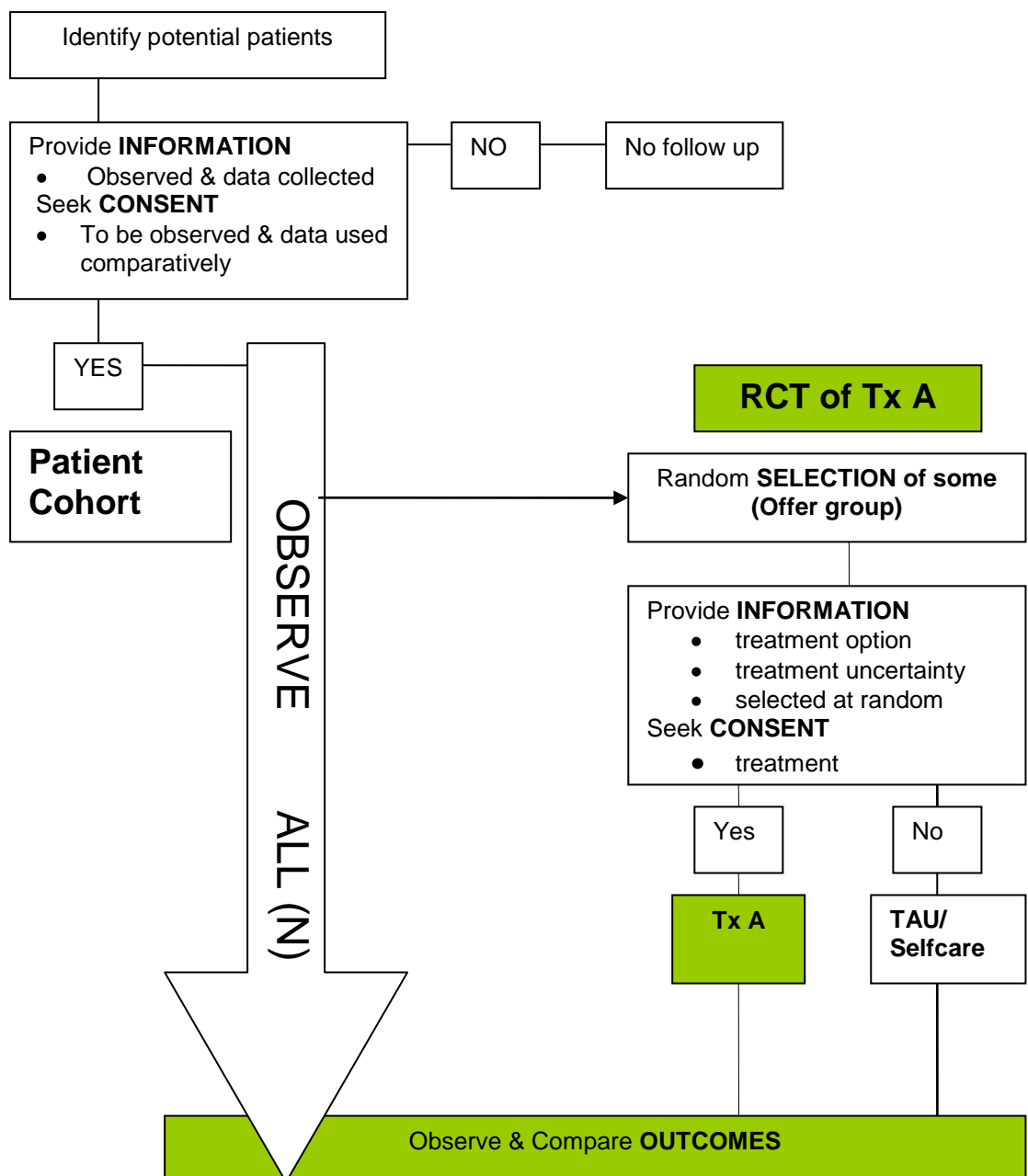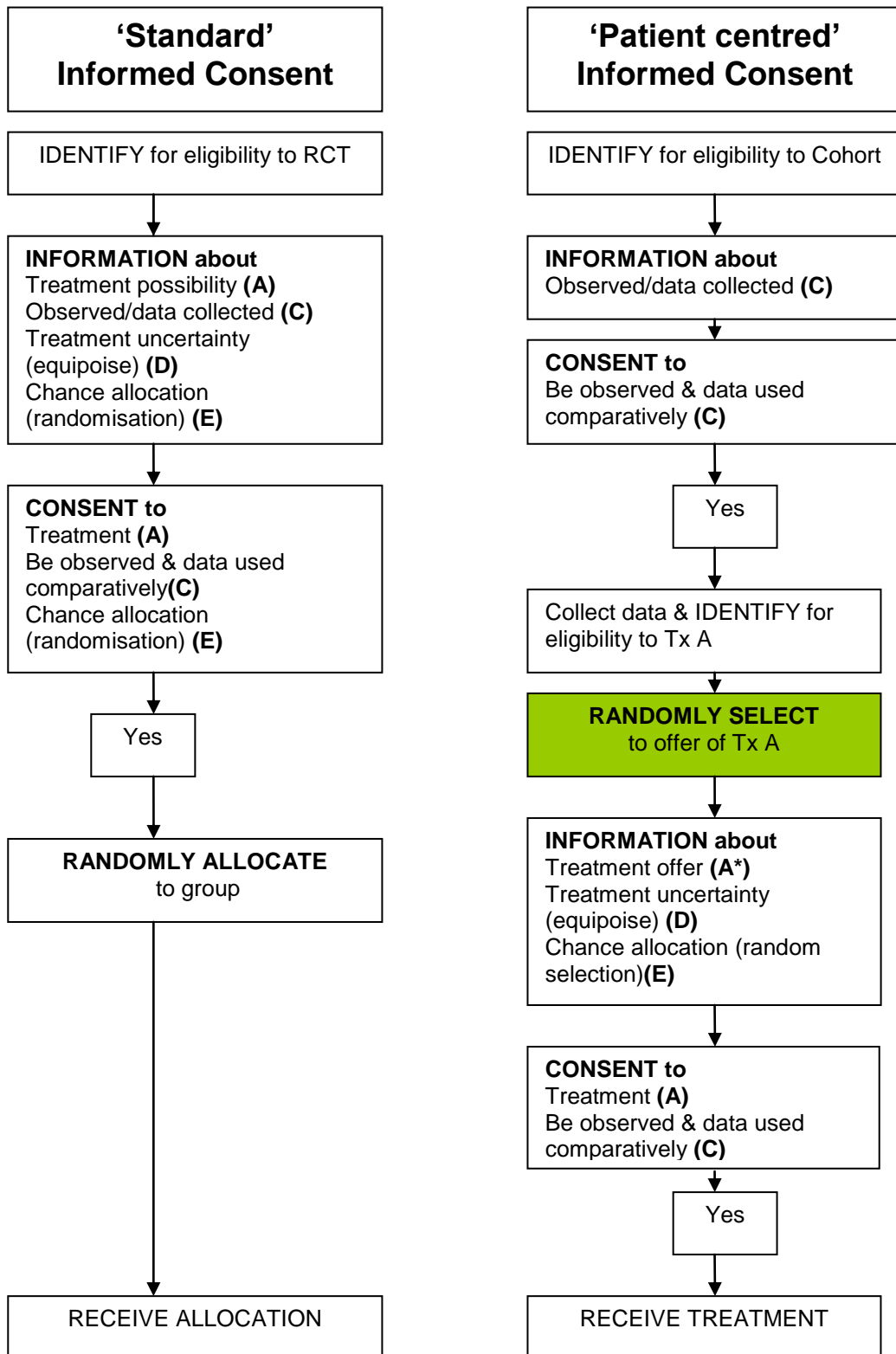
6.6.5   Uncontaminated control group

As a result of attempting to replicate the processes of routine healthcare with 'Patient centred informed consent' then (unlike standard Informed Consent), the control group is uncontaminated by information such as: 'There is a treatment and it may benefit you', 'We are not sure which treatment is best….', and 'We are going to play a game of chance'. The advantage of an uncontaminated control group is that it reduces the likelihood of dilution bias in the control group – the likelihood of those in the control group obtaining the intervention being received by the treatment group.

6.6.6   Disadvantages

Research Ethics Committees will be unfamiliar with the distinction between random selection and random allocation and the need to split the delivery of the different types of information and consent. The current norm for Research Ethics Committees is that all patients involved in research must be given 'full' information as to how they have been selected with regards to the research and whatever treatment group they are allocated to. The National Research Ethics Services (NRES) Informed Consent procedure has already been described in Chapter 4. Diagram 6.5 compares current standard NRES Informed Consent procedures for trials with the 'Patient centred informed consent' procedures for the 'Patient Cohort' RCT method. We can see that the same information is provided and the same consents are sought in both styles of Informed Consent. There are two fundamental differences however, the first difference is in the timing of the different types of information/consents, and the second difference is that in the 'Patient Cohort' RCT treatment information is about treatment that they will receive (if they accept it) rather than about treatment that they might receive (regardless of whether they want it or not).

Diagram 6.5   Comparison of informed consent procedures for RCTs

'Standard' Informed Consent	**'Patient centred' Informed Consent**
IDENTIFY for eligibility to RCT	IDENTIFY for eligibility to Cohort
INFORMATION about Treatment possibility **(A)** Observed/data collected **(C)** Treatment uncertainty (equipoise) **(D)** Chance allocation (randomisation) **(E)**	**INFORMATION about** Observed/data collected **(C)**
CONSENT to Treatment **(A)** Be observed & data used comparatively**(C)** Chance allocation (randomisation) **(E)**	**CONSENT to** Be observed & data used comparatively **(C)**
Yes	Yes
RANDOMLY ALLOCATE to group	Collect data & IDENTIFY for eligibility to Tx A
	RANDOMLY SELECT to offer of Tx A
	INFORMATION about Treatment offer **(A*)** Treatment uncertainty (equipoise) **(D)** Chance allocation (random selection)**(E)**
	CONSENT to Treatment **(A)** Be observed & data used comparatively **(C)**
	Yes
RECEIVE ALLOCATION	RECEIVE TREATMENT

6.7   Meeting the key criteria

How far does the 'Patient Cohort' RCT satisfy the twelve key criteria for appropriate trial design? This thesis argues that the design goes further towards meeting the twelve key criteria than the current standard pragmatic RCT design. Box 6.2 lists the three main features of the 'Patient Cohort' RCT design (the Cohort, Random selection of some and 'Patient centred informed consent') and its ten additional features.

Box 6.2   Features of the 'Patient Cohort' RCT design

MAIN FEATURES:

Cohort

Random Selection

Patient centred information and consent

ADDITIONAL FEATURES:

– Scoping information

– Treatment as usual

– Long term outcomes

– Multiple trials facility

– Increased comparability

– Increased statistical power

– Increased efficiency

– Uncontaminated control group

– Patient appropriate relationships

– Congruence with motives of patients and practitioners

The 'Cohort' aspect of the 'Patient Cohort' RCT design maps onto three key criteria as they enable these three criteria to be fulfilled: Pragmatic RCT (I), Findings generalisable to 'with need' population (III) and Produce short and long term outcomes (IV) however the two other main features of the design: 'Patient centred informed consent' & 'random selection' do not map directly onto any one single criterion, but instead jointly facilitate all twelve key criteria. Chapter 9 evaluates a pilot of the 'Patient Cohort' RCT design as a research tool per se, using information derived from the pilot and attempting to assess the extent to which the pilot of the design met the 12 criteria for appropriate trial design.

6.8. Comparison with alternative RCT designs

The 'Patient Cohort' RCT design has already been compared to the standard pragmatic RCT with regards to randomisation (Diagram 6.4) and Informed Consent procedures (Diagram 6.5), but how does this design compare with other RCT designs?

6.8.1. Ten study designs

Chapter 5 discussed the twelve key criteria in relation to ten RCT designs identified in an HTA report[39] (MacLehose et al., 2000). This section now compares the 'Patient Cohort' RCT design to these ten RCT designs.

6.8.2. 'Hybrid designs'

There are several key differences between the 'Patient Cohort' RCT and the four hybrid designs (Comprehensive Cohort Study, Patient preference trial, Clinician preferred treatment trial and Two stage trial).

Random selection of some vs random allocation of all

The first difference is in how randomisation is operationalised. The 'Patient Cohort' RCT operationalises randomisation as random selection of some, whereas all four hybrid designs operationalise randomisation as random allocation of all. Random selection is a feature of the 'Patient Cohort' RCT design which aims to improve both recruitment (Key Criteria III to XII) and the complexity and proper functioning of the intervention during the trial for the patient and clinician (Key Criterion II).

Consent to randomisation

The second difference is that in all four hybrid designs, consent to random allocation to groups is sought from all patients prior to randomisation, whereas in the 'Patient Cohort' RCT consent to be randomly selected is not sought prior to randomisation, although those randomly selected to a treatment group are informed post hoc. Consent to random allocation to groups in all four Hybrid RCT designs results in consent and information that is not appropriate to the patient's 'patient' status - thus Key Criteria V & VI are not met.

Consent differential

The third feature of 'hybrid designs' that differentiates them from the 'Patient Cohort' RCT design is the consent differential. Each hybrid design includes an observational arm(s) running alongside a RCT; participants in the observational arm(s) are different to those in the RCT in respect to how they have consented in that those who do **not** consent to randomisation become participants in the observational arm(s) and those who **do** consent to randomisation become participants in the RCT. Thus the two groups are not directly comparable due to a differential in the types of consents they have given.

Reduced internal validity

---

[39] This report aimed to investigate the association between methodological quality and the magnitude of estimates of effectiveness derived from RCTs and quasi-experimental and observational studies (QEOs).

The fourth difference between 'hybrid designs' and the 'Patient Cohort' RCT design is that **all** patients in the 'Patient Cohort' RCT are randomised (randomly selected or not randomly selected) thus maintaining the internal validity of the design whereas 'hybrid designs' collect data from both randomised and non randomised patients – thus reducing the internal validity of their designs (Key Criterion VIII).

Treatment preferences: strong, explicit vs any, non implicit

The fifth difference relates to treatment preferences. The Patient preference trial, the Two stage trial and the Clinician preferred treatment trial are study designs which allow patients/ clinicians with strong preferences to choose their preferred treatment or to influence treatment allocation and the assessment of 'strong preferences' is made an explicit part of each of these trial processes. The 'Patient Cohort' RCT observes but does elicit whether patients have strong, weak or fluctuating preferences, thus allowing patients & clinicians to choose their preferred treatment as they would do in routine healthcare (Key Criterion XI).

6.8.3 'RCT variants' '

MacLehose et al. (2005) describes six RCT variants: Randomised play– the-winner design, Randomised discontinuation trial, Change to open label, Placebo run-in trial, Single Randomised Consent Design, and the Double Randomised Consent Design.

Four of the six RCT variants are designs which address issues unrelated to external validity. The Randomised play– the-winner design aims to minimise the number of patients who receive the less effective treatment – an ethical/efficiency issue rather than external validity issue. The randomised discontinuation trial, Change to open label design and the placebo run-in trial each use placebo in their design and are thus the main difference is that they are designs which address the question of efficacy whereas the 'Patient Cohort' RCT design is an ultra pragmatic RCT design which addresses questions of effectiveness.

6.8.4 Randomised Consent Designs

However two of the 'RCT variants' designs – the Single Randomised Consent Design (SRCD) and the Double Randomised Consent Design (DRCD) both share a key feature with the 'Patient Cohort' RCT design – the absence of prior consent to randomisation. Not seeking consent to randomisation (and thus not providing information regarding randomisation prior to randomisation) enables many of the key criteria to be met: V (Replicate the processes of routine healthcare), VI (Patient appropriate information), VII (Patient appropriate consent), XI (Patient and practitioner preferences remain unaltered), XII (Consent procedure is not a barrier), and VIII (internal and external validity).

6.8.5 Comparison of the 'Patient Cohort' RCT' with Single Randomised Consent Designs

Non prior consent to randomisation is a central feature of both the Single Randomised Consent Design (SRCD) and the 'Patient Cohort' RCT design, however the 'Patient Cohort' RCT design

offers an evolved version of the SRCD. This evolved version differs from the SRCD in three ways.

Firstly, the 'Patient Cohort' RCT design carefully differentiates between the types of information given and the types of consents sought, and seeks to replicate the types and timings of information and consent that occur in routine processes of healthcare wherever possible. Being able to differentiate between the different types of information and consents gives clarity to discussions as to the ethics, psychological impact and science of recruiting patients into RCTs, a clarity that has been lacking in discussions about all Randomised Consent Designs.

Secondly, the 'Patient Cohort' RCT randomly selects some rather than randomly allocates all as in the SCRD. Those patients in the Cohort are not in a trial until they are randomly selected to be offered the option of **trying**[40] a treatment. Those patients in the Cohort NOT randomly selected are not in a trial but they have given consent for their data to be used comparatively – and this data is used as the comparator data when assessing the effectiveness of the intervention in the RCT.

6.8.6   The 'Adapted randomised consent (Zelen) design'

Mention must be made of the 'Adapted randomised consent (Zelen) design' (Campbell et al., 2005) (which was published after the pilot of the 'Patient Cohort' RCT design to assess the clinical and cost effectiveness of treatment by a homeopath for women with menopausal hot flushes had been put forward for ethical approval). Campbell et al., (2005) stated that the 'Adapted randomised consent (Zelen) design' was created to permit a rigorous evaluation of a complex package of care and to overcome ethical and methodological problems associated with the standard Zelen design conducting trials of desirable interventions which might lead to post randomisation attrition in those who are not randomly allocated to the desirable intervention. The 'Adapted randomised consent (Zelen) design' used a single randomised consent design where consent was sought only from the intervention group post randomisation, nested within an observational study for which prior consent was obtained. The 'Adapted randomised consent (Zelen) design' was described thus:

> *'Eligible patients were first consented to a one year observational study of their arthritis; they were then subsequently randomly allocated into intervention and control arms. Those in the intervention arm were then asked if they were willing to participate in a further study involving regular sessions with a physiotherapist. Those in the control arm were not told about this, but were followed up as agreed'* (Campbell et al., 2005).

The Adapted randomised consent (Zelen) design is essentially the same design as the 'Patient Cohort' RCT in that both use:

– the initial use of an observational cohort
– staged information & consent (i.e. no information was given to those patients who were not allocated to the intervention and 'treatment' information was given after randomisation).

---

[40] Both the terms 'trial' and 'try' have the same root 'trier' meaning to sift (Old French)

However, there are three important differences between how the 'Adapted randomised consent design' and the 'Patient Cohort' RCT design have been conceptualised.

(1) The 'Patient Cohort' RCT design utilises a Cohort which is seen as a facility for obtaining long term as well as short term outcomes as well as a facility for testing multiple interventions – multiple RCTs – and not just a discrete time bounded (SAS style) RCT to test a single intervention as described by Campbell.

(2) The 'Patient Cohort' RCT design operationalises randomisation as *'random selection of some'* rather than the standard *'random allocation of all'* .

(3) The 'Patient Cohort' RCT design elucidates the different types of information and consent e.g. information/consent to *Treatment offer (A*), Treatment uncertainty (equipoise) (D), Chance allocation (random selection)(E)* and emphasises the importance of ensuring that their delivery is as similar to that of routine clinical care with regards to both timing (pre or post random selection) and b) to whom the information/consent is given/sought.

6.9   Testing the design

This chapter has described the 'Patient Cohort' RCT design – a clinical trial design which is shaped around the '*needs and preferences of individual patients'* www.nhs.uk/coreprinciples [accessed 24.3.08](). This thesis suggests that the 'Patient Cohort' RCT design is a clinical trial design that will produce results that can inform real world decision making for publicly funded healthcare systems, and that it is an appropriate trial design for pragmatic RCTs (Key Criterion III) and that this design has both internal and external validity (Key Criterion VIII). The evidence for this assertion thus far has been theoretical. To assess just how well the 'Patient Cohort' RCT design can meet all twelve key criteria needs further research, the following chapters report the testing and evaluation of the design. Chapter 7 reports the conduct of the preparatory work needed to conduct a pilot 'Patient Cohort' RCT, chapter 8 reports the results of a pilot of the 'Patient Cohort' RCT design and chapter 9 evaluates the design.

Chapter 7

Identifying the Cohort: the Women's midlife health survey

7.1   Introduction

At the beginning of this thesis the research question was: *"What type of clinical trial design can provide the information needed to make decisions about the provision of homeopathy in a publicly funded healthcare system?"* Twelve key criteria for appropriate trial design were derived from the perspectives of four stakeholders. No existing clinical trial designs met all 12 criteria therefore the 'Patient Cohort' RCT design was constructed in an attempt to meet all 12 criteria. The next step was to use the 'Patient Cohort' RCT design in the real world, to address a real world research question. Chapters 7 & 8 report the design and conduct of the primary clinical research which took place over a three year period from 2005 to 2008.

7.1.1   Aim
The aim of chapter 7 is to identify the information needed in order to pilot the 'Patient Cohort' RCT design.

7.2   Scoping for the trial

Chapter 3 identified an increase in the number of UK women with menopausal hot flushes who either could not or would not use HRT as a treatment for their hot flushes. This unmet need had increased after the publication of the three studies (MWS, HERS & WHI) during 2002/3, and the subsequent changes in clinical guidelines. In early 2005, a literature search revealed no up-to-date information on women's attitudes towards, and experiences of, HRT or the type

and prevalence of alternative treatments to HRT that were being used to treat hot flushes. Information was needed to assess the extent of this unmet need. An RCT of treatment by a homeopath was being considered, but before any trial could be conducted, the following scoping information was required:

A. Prevalence and severity of hot flushes and other symptoms of the menopause in the local female population
B. Types of treatments currently used by women to help with their menopausal hot flushes
C. HRT: Women's experiences of and attitudes towards

7.3 Identifying the Cohort

The application of the 'Patient Cohort' RCT design required the identification of a cohort of people with the condition of interest (which in this instance is menopausal hot flushes). However, it was unclear as to what type of cohort was needed, whether this type of cohort already exist and if not, how such a cohort be created.

7.3.1 Types of Cohorts

In statistics, a cohort is a group of subjects, defined by experiencing an event in a particular time span and a 'cohort study' is a study design *'where a selected population is studied over time to investigate the effect of a particular variable on health outcomes'* (Saks & Allsop, 2007). Joining a cohort study can start at birth e.g. all those born during a certain time period such as the 1946 British Birth Cohort Study (Mishra et al., 2007) or at the onset of a particular disease such as the **Scottish Motor Neurone Disease Register (Forbes et al., 2004).** Potential members of a cohort can be identified as result of a population based survey or as a result of seeking treatment for the condition in question. Since one of the key criteria is 'a pragmatic RCT' then, in order to provide information useful to the NHS, either an NHS based cohort or a cohort whose results can be easily extrapolated to the NHS is required. Unlike some disease conditions such as Huntington's disease (http://hdresearch.ucl.ac.uk/registry.html), there is no easily identifiable existing cohort of women with hot flushes despite the prevalence of the condition.

7.3.2 Sample frame for the cohort

Since there was no existing 'ready made' 'Hot Flush' cohort, one needed to be created for the purposes of this research. In order to gain up-to-date scoping information and a broad picture of the current 'with need' population, women registered with NHS GP practices in Sheffield were approached. A non treatment seeking sample frame will provide a more accurate NHS perspective on the actual needs of women in this age group than a treatment seeking sample as some women do not seek treatment despite being 'with need' for a variety of reasons e.g.

expectation that the treatment that will be prescribed will be HRT, so if they do not want HRT they will not consult their GP.

7.4.   Methods

The scoping for the condition and the treatment as well as identifying and recruiting the cohort were all achieved by means of one postal questionnaire survey. This was conducted in Sheffield, a large city in the north of England with a socioeconomically diverse population. This survey utilised a cross sectional survey design, with data collected from a local non clinical (population) sample of women aged 45 – 64 years old.

7.4.1   Survey objectives
The objectives of the survey were to produce up-to-date information on the:
   A. Prevalence and severity of hot flushes and other symptoms of the menopause in the local female population
   B. Types of treatments currently used by women to help with their menopausal hot flushes
   C. Women's attitudes towards HRT and their experiences of HRT
And also to:
   D. Identify women suitable for the 'Hot Flush' cohort

7.4.2   Study sample
The target population was all women aged 45 – 64 in Sheffield. Forty five years is the earliest accepted possible age to start the menopause 'normally'; before 45 is termed 'early' menopause. Most menopause research targets 45 to 55 year olds, but many women in their late 50s, 60s and occasionally even in their 70s, are still suffering from vasomotor symptoms, including those who have had to stop HRT (Ockene et al., 2005; Grady et al., 2002; Ettinger et al., 2003). In order to identify all menopausal and postmenopausal women who were experiencing hot flushes, the age range of the target population would ideally have had no upper limit. But since the prevalence of hot flushes diminishes with age, including women age 65 to 80 in the survey would have produced a very low yield, so the age range chosen was 45-64. Although this age range would not capture all women, it would still capture the experiences of the majority of women with vasomotor symptoms.

7.4.3   Sampling method
A two stage sampling method was chosen. Firstly GP practices were selected and then women were randomly selected from these practices. Practices were chosen in order to be broadly representative of the demographics of Sheffield. Six GP practices were identified using a

purposive sampling method. In order to recruit a representative sample of women, practices were picked to reflect the variety of socio-economic profiles and geographical locations of Sheffield.

7.4.4   Balancing the sample

Deprivation was seen to be a key variable that needed to be reflected in the sample due to its strong relationship to poor health (Carstairs, 1995), thus in order to ensure that a balanced sample of GP practices was picked, the Index of Multiple Deprivation 2000 was identified for the area that each practice covered. Index of Multiple Deprivation data is published by the Department of Environment, Transport and Regions (DETR) www.sheffield.nhs.uk/healthdata/deprivation and the description of how the Index was created can be found at: http://www.renewal.net/Documents/RNET/Research/Indicesofdeprivation.pdf 'Multiple deprivation' cannot be directly measured, but is a combination of several dimensions of deprivation, which can to some extent be measured. The Index of Multiple Deprivation (IMD) is a ward level composite score of six separate dimensions or domains of deprivation – income (25%) employment (25%), health deprivation & disability (15%), educational skills and training deprivation (15%), housing deprivation (10%), and geographic access to services (10%). The scores range from 0 to 100, with the higher the score, the more deprived the ward is.

7.4.5   Deprivation in Sheffield

Sheffield local authority ranks as one of the more deprived local authorities in England, coming in as the 60th (out of 354) most deprived local authority in England. In comparison, Tower Hamlets which is the most deprived local authority in England has a mean ward level IMD score of 60.0, and Horsham, one of the least deprived local authorities, has a mean ward level IMD score of 6.9. The mean ward level IMD score for Sheffield local authority is 34.0 http://www.statistics.gov.uk/CCI/SearchRes.asp?term=IMD+2000 (accessed 30.8.08).

7.4.6   GP practices

GP practices were sought which had a variety of IMD scores and had practice managers and GPs willing to participate. Only a rough estimate of the IMD score of the area that each GP practice covered was possible, as the boundaries of the electoral wards and the boundaries of the areas that the practices drew their patients from were not always the same and some GP practices drew their patients from more than one electoral ward. It was not practical in this study to calculate the exact proportions taken from each electoral ward.

Ten GP practices were selected and approached through phone calls, letters (Appendix B) and emails to the practice managers. Six out of ten practices approached agreed to participate. A financial incentive was offered to the practice in the form of a £30 Marks & Spencer gift voucher. All administrative demands on the practice manager were kept to a minimum and a report of the findings for each GP practice was offered in order to make participation in the survey more attractive.

7.4.7   Description of GP practices

The six GP practices covered electoral wards with a variety of IMD scores ranging from areas of very low deprivation (IMD score = 4.7 & 18.1) to areas of very high deprivation (IMD = 70.8 & 73.4). Table 7.1 below describes the GP practices included, the electoral ward where the majority of patients registered at that practice live, the IMD scores for each ward and the number of women aged 45 – 64 permanently registered with each practice. IMD scores were grouped into three bands: low, medium or high.

Table 7.1   **GP practices and Index of Multiple Deprivation (IMD) scores**

Practice name	Electoral Wards	IMD score (0 – 100)	IMD band	Number of women aged 45 - 64
Deepcar Medical Centre	Deepcar	18.1	Low	603
Ecclesall Medical Centre	Ecclesall Netheredge	4.7 17.9	Low	1,139 [$]
Upperthorpe Medical Centre	Upperthorpe	31.9	Medium	
Birley Medical Centre	Birley	32.1	Medium	1,039
Foxhill Medical Centre	Owlerton Southey Green	49.0 73.4	High	694
Dovercourt surgery	Castle, Manor Park	63.4 70.8 68.9	High	424

[$] Upperthorpe and Ecclesall GP practices have combined to have a single practice manager and a single patient database and were unable to provide practice specific data on numbers.

7.4.8   Sample of women

The population from which the study sample was chosen was all women aged between 45 and 64 who were registered with one of the six GP practices in Sheffield and were living permanently at their home address. Since the mean IMD score of all six GP practices added together was 34.8 and the Sheffield mean IMD score is 34.0 it is likely that this is a fairly representative sample frame of the women of Sheffield.

The sample size was calculated by estimating the number of women needed for the proposed pilot trial. We assumed that 5% -10% of the responders would meet all the criteria for the pilot trial, these had not been finalised at this point, but we knew would include: severe/frequent hot flushes. We also assumed a 60 - 70% response rate to the questionnaire. So in order to have

40 to 50 women willing to participate in the pilot trial, 1,200 questionnaires would need to be sent out, with an expected return of 720, of whom 36-72 women would meet the trial criteria. Thus 1,200 women were selected at random from 3,899 women registered with the six GP practices selected. The study sample represents a third of women registered with these six GP practices. 200 women were selected at random from each practice list using a random number generator function on a calculator (practice lists varied in size between 424 and 1,039).

7.4.9 Questionnaire

The research method used was postal self completed questionnaires. There was no existing questionnaire that covered all of the research questions, so a new questionnaire was designed. To avoid eliciting stereotypical views of the menopause, the survey was described as the Women's Midlife Health Questionnaire. Almost all experts in survey and questionnaire design recommend the use of reminders (McColl et al., 2001). Although two or three reminders would have increased the response rate, the NHS ethics committee vetoed the use of more than one reminder.

The questionnaire (Appendix D) was 6 sides of A4 with a total of 47 questions covering: age, menstrual/menopausal status, general menopause symptoms, incidence, frequency and severity of hot flushes and night sweats, types of activity (gardening, yoga, walking etc), types of alternative therapists consulted, dietary changes, effectiveness of alternative therapy, activity, diet or therapy on hot flushes, current medication usage (prescribed and over the counter), HRT usage and status and attitudes to HRT, reasons for stopping HRT, length of time HRT taken, and side effects of HRT.

7.4.10 Types of questions

Postal questionnaires have to be simple and straightforward to preclude non- response through uncertainty (Stone, 1993; Edwards et al., 2002; McColl et al., 2001) and well designed closed questions are more straightforward and simpler to answer than open questions which ask respondents how they feel or what they believe about something. In the questionnaire (Appendix D) there were forty three 'closed' questions addressing specific issues. Questions were mainly single or multiple choice closed format questions. Four 'open' questions were included, asking respondents how they perceived the effectiveness of their activity, diet or alternative therapy on their hot flushes, and whether they had any comments about the menopause or thoughts on how best to treat the symptoms of the menopause.

7.4.11 Measuring hot flushes

The first page of the questionnaire (Appendix D) used the Greene Climacteric Scale (Greene, 1998). This is a commonly used measure of the menopause in observational research (Porter et al., 1996), and is used to elicit type and severity of menopausal symptoms. The Greene Climacteric Scale (GCS) is a validated, brief, self administered set of 21 questions of core climacteric/ menopausal symptoms or complaints, women are asked to score *'how bothered'*

they are by each of the 21 symptoms – 'not at all' (0) – 'a little' (1) – 'quite a bit' (2) – 'extremely' (3).

A brief review of the literature reporting RCTs of interventions for hot flushes revealed that '*how bothered*' women were by their hot flushes, as measured by the GCS or any other outcome measure, was rarely used. Instead, the most commonly used primary outcome measure for RCTs was the frequency and severity of hot flushes, thus this would be the primary outcome measure for the RCT. The primary inclusion criterion for the majority of RCTs was *'14 or more hot flushes a week'* (Loprinzi et al., 2000; Stearns et al., 2000; Van Patten et al., 2002); thus if the results of the planned pilot RCT were to be comparable to RCTs of other hot flush interventions then *14 or more hot flushes a week* would need to be the inclusion criteria for the proposed trial. So as well as the GCS, the questionnaire needed to elicit information as to the frequency and severity of the women's hot flushes; therefore the hot flush frequency and severity questions were introduced. These outcome measures are discussed further in section 8.2.8.

7.4.12   Administering the survey

Previous researchers' experience was taken into account in the design and administration of the questionnaires (Stone, 1993; Edwards et al., 2002; McColl et al., 2001). High survey response rates are desirable as they increase the precision of parameter estimates and reduce the risk of non-response bias (McColl et al., 2001). In order to achieve the highest response rate possible, the questionnaire was kept short and used everyday rather than specialist language (Edwards et al., 2002). Personally sensitive questions such as questions on vaginal dryness (a common symptom of the menopause) were excluded as it was felt such a question may put off some potential respondents (Edwards et al., 2002). The researcher chose a questionnaire colour (pink) that would be well received by this patient group. In designing the questions, the proposed outcome measures of the planned pilot study were used wherever possible. It is generally recommended that presentation of written and visual information in questionnaire design is as consistent as possible (McColl et al., 2001); however multiple validated outcome measures were incorporated into the questionnaires each of which had different styles of presentation. Thus the questionnaire was quite varied in the question presentation. The questionnaires were piloted with 15 women. Completion time for the questionnaire was 4 – 5 minutes. Advice and comments on the layout, logic of the flow of questions and clarity of phrasing were noted, and the questionnaire was redrafted.

Each GP practice adapted the template covering letter to their practice (Appendix C) and printed off a list of names, ages and addresses of all the female patients in the age group 45 – 64 (as of 1.10.05) who were permanently registered with their practice. The covering letter on GP practice headed notepaper was signed by the practice manager or GP of the respondent's GP practice. The covering letter asked each woman if they were willing to cooperate with researchers at the University of Sheffield in research on women's midlife health. Reference to the University has been shown to increase the credibility of the research and thereby increase

response rates (Edwards et al., 2002). The covering letter gave other information about the survey including the offer of a reward for each completed returned questionnaire in the form of entry into a free prize draw for 10 M&S vouchers (value £25 each). Financial incentives have been shown to substantially improve response rates to postal questionnaires generally (Edwards et al., 2002), although Nakash et al. (2006) found no evidence that this is true for postal questionnaires for healthcare studies.

Each letter was personalised by hand writing the respondent's first name at the beginning of the letter, as personalised letters and questionnaires increase response (Edwards et al., 2002) and envelopes were personalised by names and addresses being hand written to each of the 1,200 women. Postage stamps rather than prepaid envelopes were used to make the envelope appear less official and more personal and thus help improve the response rate (Lavelle et al., 2008). The pink 6 sided WMHQ1 (Appendix D) was enclosed along with the personalised covering letter. A business reply envelope for the return of the questionnaire with the postage prepaid was used in order to minimise the monetary cost to the responder (McColl et al. 2001). Non respondents were sent one reminder letter with a further copy of the questionnaire after four weeks as this has been shown to improve response rates (Edwards et al., 2002).

7.4.13 Approvals

In October 2005 Governance was granted by Sheffield NHS Health & Social Research Consortium (Reference ZE91) and NHS Ethical approval for the survey was granted on 5.8.05 by North Sheffield NHS Research Ethics Committee (REC) reference number 05/Q2308/94.

7.4.14 Analysis

In order to ascertain the extent of any non-response bias, the responders to the questionnaire were analysed with regards to their GP practice and IMD band. For purposes of analysis patients were divided into four different groups (in accordance the commonly used World Health Organisation (1996) definitions of the menopause): regular menses, irregular menses in the last 12 months, no menses in the last 12 months, hysterectomy.

The analysis of key variables was divided into four sections:

A. Menopausal symptoms: women reported whether they were currently experiencing hot flushes or night sweats and, if they were, whether they were having 14 or more per week. The severity of hot flushes and night sweats was reported as: mild, moderate, severe or very severe. General menopause type symptoms were reported using the Greene Climacteric Scale (GCS) score and a total GCS score was calculated.

B. Types of treatment used by women: women reported the overall number of medications they were currently taking, both prescribed and self-prescribed, and the number and type of menopause specific medications they were taking.

C. HRT use: women reported HRT use (current/ever), duration of use, reason for stopping, whether they had experienced side effects from HRT and reasons for stopping HRT.

D. A possible Hot Flush cohort: the following characteristics of women with severe/very severe or frequent hot flushes or night sweats are reported: age, menopausal status, IMD

band, frequency and severity of hot flushes & night sweats, medication (prescribed and self-prescribed), HRT use and whether they had experienced HRT side effects.

7.5   Results

7.5.1   Response rate

1,214 women were identified and each sent a letter (Appendix C) and questionnaire (Appendix D). 862 questionnaires were returned of which 668 questionnaires were received after the first mailing. After one reminder a further 194 questionnaires were received. Five questionnaires were excluded as women had answered none of the questions concerning hot flushes or night sweats. One woman was in care and thus not permanently resident at her home address. This left 856 valid questionnaires giving a 70.6% (856/1,213) response rate. Response rates varied between practices (Table 7.2) and were higher from patients registered with GP practices in areas of low deprivation (76.5% & 77.9%) than in areas of average or high deprivation (64.5% to 68.9%). This meant that women registered with GPs in areas of low deprivation made up more of the responders (36.5%) than women from areas of medium deprivation (31.7%) or high deprivation (31.9%). Higher response rates were associated with areas of lower deprivations as measured by the IMD band (Spearman's rank correlation coefficient r = -0.74 p-value of 0.01).

Table 7.2   Response rate by GP practice and IMD band

GP practice	IMD band	Questionnaires returned/sent	Response rate
Deepcar	Low	159/204	77.9%
Ecclesall	Low	153/200	76.5%
Upperthorpe	Medium	135/200	67.5%
Birley	Medium	136/201	67.7%
Foxhill	High	144/209	68.9%
Dovercourt	High	129/200	64.5%

7.5.2   Description of responders

Table 7.3 presents an overview of the characteristics of responders. The mean age of responders was 54.0. The largest category of women were post menopausal women (no menses in last 12 months), and the second largest were those who had a hysterectomy. There were more responders from the age groups 45 – 49 and 54-59 than the 50-54 and 60-64 age groups. This is probably due to a characteristic of the underlying sample from which women were randomly selected as the UK government national statistics website

(http://www.statistics.gov.uk/cci/nugget.asp?ID=6 accessed 27.8.08) shows a corresponding bulge in these two age ranges.

Table 7.3   **Characteristics of responders**

Characteristics	All responders N=856
Age, yrs (as of Nov 2005) mean & SD	54.0 (5.50)
Menopausal status	
Regular menses	143 [16.7%]
Irregular menses	119 [13.9%]
No menses in last 12 months	400 [46.7%]
Hysterectomy	168 [19.6%]
Not reported$	26 [3.0%]
IMD Band	
Low deprivation	312 [36.5%]
Medium deprivation	271 [31.7%]
High deprivation	273 [31.8%]
Hot flushes	442/856 [51.6%]
14 or more hot flushes per week	133/442 [30%]
Hot flushes – mild or moderate	368/449 [82%]
Hot flushes - severe or very severe	81/449 [18%]
Night sweats	430/856 [50.2%]
14 or more night sweats per week	91/430 [21.2%]
Night sweats - mild or moderate	357/445 [80.2%]
Night sweats – severe or very severe	88/445 [19.8%]
GCS total score (0-63) mean (SD)	15.07 (10.45)
Medication (one or more)	561/856 [65%]
Number of medications	1,978/856
Number of prescribed medications	1,403/1,978 [70.9%]
Number of self-prescribed medications	575/1,978 [29.1%]
Medication total (MCQ) mean	2.31
Prescribed medication mean	1.64
Self-prescribed medication mean	0.29
HRT ever used (yes)	269/856 [31.4%]
HRT side effect any (yes)	165/269 [61.3%]

Data presented as mean & (SD) or n [%]

$Women who did not report their menopausal status were much more likely to be in the 60-64 age group, (Chi-Squared p-value 0.006); the reason for this was probably lack of familiarity with the terms used as these women would usually report the number of years since their last period.

The average age of the menopause is 51 (BMS, 2002) therefore given the 45-64 age range of the sample one would expect 30% of women aged 45 – 64 to be pre- or peri-menopausal and the actual figure is 30.6%. So responders appear to be representative in regards to their menopausal status.

7.5.3 Hot flushes

Over half (51.6%, 442/856) of all responders reported that they were currently experiencing one or more hot flushes each week (Table 7.3). As the primary inclusion criteria for RCTs of hot flush treatments is 14 or more hot flushes per week, information on hot flush frequency was collected. 449 women reported how mild or severe their hot flushes were but only 442 reported the actual number of hot flushes. Of the 442 women who reported experiencing hot flushes, almost a third of women (30% 133/442) reported having 14 or more hot flushes a week. The majority of women, however, described their hot flushes as mild or moderate (82% 368/449) rather than severe or very severe.

7.5.4 Night sweats

445 women reported the mildness or severity of their night sweats but only 430 women reported the frequency of their night sweats (Table 7.3). A similar number of women reported currently experiencing night sweats (50.2%, 430/856) as reported hot flushes, but only one fifth (19.8%, 88/445) of women who experienced night sweats described their night sweats as severe or very severe.

7.5.5 Medication use

Women were asked to list all their medications, including vitamins, mineral supplements, dietary supplements, herbal or homeopathic remedies. Two thirds (65% 561/856) of all responders reported taking one or more medications either prescribed or self-prescribed. The mean number of medications taken was 2.31 (1,978/856). Over two thirds (70.9% 1,403/1,978) of the medications reported by women were prescribed (a mean of 1.64 each). Over a quarter (29.1%, 575/1,978) were self-prescribed (a mean of 0.29 each) and were for a wide variety of medical conditions and symptoms. These reported figures may be below the real unadjusted figures as 5% of women who reported taking medication did not give any medication details.

7.5.6 'Menopause' medications

The survey looked to see if there was an obvious comparator to treatment by a homeopath so the survey asked women to report the reason for taking each medication. There were no ready made categories of answers given in the questionnaire from women could choose thus the answers women included a wide variety of responses. Women reported taking medication for the 'menopause' 'peri-menopause', 'hot flushes', 'suppress symptoms of menopause', 'hot sweats', 'HRT' 'instead of HRT' 'had ovaries removed'. This information is all reported together in Table 7.4 using the three headings listed in the BMS handbook for menopausal symptoms'

treatment strategies: oestrogen based HRT, non oestrogen based HRT, and complementary & alternative therapies.

81 women reported taking 104 'menopause' medications which included 49 different types of medication (Table 7.4). 34 women reported taking oestrogen based HRT and 6 women reported taking non oestrogen based HRT. 61% (64/104) of women reported taking medications which came under the BMS classification of 'Complementary & alternative therapies'.

Table 7.4   Menopause medications

Type	Types	Women
Oestrogen based HRT		
HRT - oestrogen or oestrogen combined with progesterone (tablets, patches, IUDs, gels)	13	34
Non oestrogen based HRT		
Dixarit, DHEA, clonidine, steroids	4	6
Complementary & alternative therapies		
1. Over the counter (OTC) combination remedies		
Combinations of vitamins and minerals packaged for 'relief of menopause symptoms' (menopace, confiance, flashfighters, meno x, vita woman)	7	7
2. Herbal remedies		
Singles: black cohosh (6 women), sage, red clover, agnus castus **Combinations**: proprietary kalms, or herbalist prescribed combinations such as cimicifuga/betula/trifolium ……)	12	23
3. Homeopathic medicines		
Hypericum, Nat Mur	2	2
4. Food supplements		
Evening primrose oil (13 women), soya isoflavones (6 women), 'aria', starflower oil, flaxseed oil, multivitamins… – prescribed medicines were evening primrose oil & calcium.	11	32

7.5.7   Oestrogen based HRT

The first BMS category is oestrogen based HRT; 34 women reported taking 14 different types of oestrogen or oestrogen combined with progesterone (tablets, patches, IUDs or gels). The fact that 64 women ticked 'yes' to the question 'are you currently taking HRT', yet only 34 women reported the type of HRT that they were taking in the medication question, signals to us that the information on medication reported in 7.5.5 – 7.5.9 is only a partial representation of actual medication taken. More details about women's experiences of HRT is reported in 7.5.11.

7.5.8   Non oestrogen based HRT

The second category in the BMS handbook is 'non oestrogen based HRT pharmaceuticals', of which six women reported taking four different types (Dixarit, DHEA, clonidine, steroids) (Table 7.4).

7.5.9   Complementary & alternative therapies:

The third category is 'complementary & alternative therapies' of which 64 women reported taking 'complementary therapies' medication (Table 7.4). Seven women took over the counter (OTC) combinations of vitamins and minerals packaged for 'relief of menopause symptoms', 23 women took herbal remedies (either single or combinations) which were obtained either OTC or from consultations with herbalists. Two women reported using homeopathic remedies. The largest category was those women who were taking what are classed as food supplements: evening primrose oil (13), soya isoflavones (6) including 'aria', starflower oil, flaxseed oil, multivitamins). Most of these were self-prescribed; however evening primrose oil & calcium were prescribed.

7.5.10   Visits to alternative therapists

Women who reported experiencing hot flushes were asked if they had had effective treatment for hot flushes from an alternative therapist. 23 women reported effective treatment for hot flushes from alternative therapists (herbalist =10, homeopath = 3, acupuncturist = 3, reflexologist = 2, more than one i.e. acupuncture & Herbalism = 5). If this question had been asked of all women, and not just those who were experiencing hot flushes at the time they received the questionnaire, then fuller information would have been obtained.

7.5.11   HRT: Use & duration

In order to understand women's experience of HRT, and attitudes towards HRT, the questionnaire asked women a series of questions: have you ever taken HRT, are there any medical reasons why you cannot take HRT, would you consider taking HRT in the future, are you currently taking HRT, is stopping HRT important, how long have you/did you take HRT, have you ever experienced side effects. Much of the information from these questions is reported in tables 7.5 & 7.6.

Almost a third 31.4% (269/856) of all responders had ever taken HRT yet only 64 women reported being current users, over half (57.8% 37/64) of whom had been taking it for over five years. The largest groups of current HRT users were those women who had had a hysterectomy (28/64, 43.8%) and post menopausal women (18/64, 28.1%). Interestingly, almost half (30/64) of those women who were taking HRT were still experiencing hot flushes/night sweats.

269 women reported having taken HRT but only 254/269 reported the amount of time that they had taken HRT. Over half of women (56.7% 144/254) who had ever taken HRT had taken it for

less than five years. 43.3% (110/254) of women had taken HRT for five years or more and 14.6% (37/254) reported having taken HRT for ten years or more.

Table 7.5   **Characteristics of HRT users**

All responders	N= 856	%
Current users*	64*/856	7.5
Regular menses	12/64	18.8
Irregular menses	4/64	6.3
No menses in last 12 months	18/64	28.1
Hysterectomy	28/64	43.8
Ever taken HRT	269/856	31.4
Duration of use of HRT	254/856	
Less than 5 years	144/254	56.7
More than 5 years	110/254	43.3
More than 10 years	37/254	14.6

* 2 women did not report their menopausal status

7.5.12 HRT: Side effects

61.3% (165/269) of women who had taken HRT reported having experienced side effects from HRT. There was a wide range of side effects reported. The most common side effect was weight gain, which was reported by 33.3% (94/269) of all women who had taken HRT; breast tenderness was reported by 18.5% of women (50/269) and headaches by 16% of women 44/269. Table 7.6 lists the full range of symptoms reported by women, the majority of which are known side effects of HRT (British National Formulary, 2000).

7.5.13 Reasons for stopping & non takers

Three quarters (76.2%, 205/269) of women who had ever taken HRT reported having stopped it. Of those women who reported a reason for stopping 39.3% stopped due to concerns about the risks or long term side effects, 32.2% stopped due to side effects or health problems from HRT and 13.3% stated they stopped it as it was no longer required.
Of the 469 women who reported currently experiencing hot flushes or night sweats, a quarter (127/469) stated that they could not take HRT or would not take HRT due to concerns about the risks or long term side effects and almost a quarter (112/469) reported having experienced 'health problems from HRT'.

Table 7.6   **HRT side effects**

Side effect reported	Numbers of women n=269
Weight gain	94 (34.9%)
Breast tenderness	50 (18.6%)
Headaches	44 (16.4%)
Fatigue	29 (10.8%)
Anxiety	27(10.0%)
PMT type symptoms	15 (5.6%)
Excessive bleeding	8 (3.0%)
Mental confusion	7 (2.6%)
Raised BP	3 (1.1%)
Skin rashes	3 (1.1%)
Leg swelling, pains, spasms	4 (1.5%)
Heavier periods (2), DVT (2), allergic reactions (2), breast lumps (2), migraines (2), sickness or nausea (2), Nose bleeds(1), stomach pains (1), bloating (1), depression (1), breathlessness (1), hair loss (1), dizziness (1).	19 (7.0%)

7.5.14 A possible 'Hot Flush' Cohort?

One of the aims of the survey was to identify patients for the cohort of women with hot flushes.
These women would need to be experiencing 14 or more hot flushes a week and willing to fill in
a further health questionnaire. The survey identified 131 women who were experiencing 14 or
more hot flushes per week. Table 7.7 reports the characteristics of all responders to WMHQ1
who make up a possible 'Hot Flush' Cohort.

Comparison of the possible 'Hot Flush' Cohort and all responders to WMHQ1 reveals they both
had a similar mean age and took similar amounts of prescribed medication. However, as
expected there were many differences between the possible 'Hot Flush' Cohort and all
responders to WMHQ1. Women in the possible 'Hot Flush' Cohort were much less likely to be
having regular menses, more likely to have severe or very severe hot flushes (Chi squared p
value 0.00), more likely to have severe or very severe night sweats (Chi squared p value 0.00),
more likely to have ever used HRT (Chi squared p value 0.00) and more likely to have reported
side effects from HRT (Chi squared p value 0.00). There was trend for cohort patients to come
from a GP practice in an area of high deprivation (as measured by the IMD score of the
electoral ward) (p value 0.07).

Table 7.7   Characteristics of the possible 'Hot Flush' Cohort

Characteristics	Possible 'Hot Flush' Cohort n= 131	All patients n=856	P values
Age, yrs (as of Nov 2005)	54.21 [4.37]	54.0 [5.50]	
Menopausal status			
Regular menses	3 [2.3%]	143 [16.7%]	0.00[#]
Irregular menses	24 [8.3%]	119 [13.9%]	0.07[#]
No menses in last 12 months	69 [52.7%]	400 [46.7%]	0.06[#]
Hysterectomy	29 [22.1%]	168 [19.6%]	0.20[#]
Not reported[$]	6 [4.6%]	26 [3.0%]	
IMD Band			
Low deprivation	39 [29.5%]	312 [36.5%]	0.07[#]
Medium deprivation	43 [32.6%]	271 [31.7%]	0.84[#]
High deprivation	50 [37.9%]	273 [31.8%]	0.10[#]
Hot flushes		442/856 [51.6%]	
14 or more hot flushes per week	131 [100%]	133/442 [30%]	0.00[#]
Hot flushes – mild or moderate	78/131 [60%]	368/449 [82%]	
Hot flushes - severe or very severe	53/131 [40%]	81/449 [18%]	0.00[#]
Night sweats		430/856 [50.2%]	
14 or more night sweats per week	71/132 [53.7%]	91/430 [21.2%]	0.00[#]
Night sweats - mild or moderate	73/132 [55.3%]	357/445 [80.2%]	
Night sweats – severe/ very severe	53/132 [40.1%]	88/445 [19.8%]	0.00[#]
GCS total score (0-63) mean	41.42 (12.32)	15.07 (10.45)	0.00[$]
Medication (one or more)		561/856 [65%]	
Number of medications	323	1,978	0.49[#]
Number of prescribed medications	228	1,403/1,978 [70.9%]	0.56[$]
Number of self-prescribed medications	95	575/1,978 [29.1%]	
Medication total (MCQ) mean	2.45 (2.44)	2.31	0.45[$]
Prescribed medication mean	1.73 (2.17)	1.64	0.56[$]
Self-prescribed medication mean	0.72 (1.29)	0.67	0.66[$]
HRT ever used (yes)	65/132 [49.2%]	269/856 [31.4%]	0.00[#]
HRT side effect any (yes)	43/132 [32.6%]	165/269 [61.3%]	0.00[#]

Data presented as mean & (SD) or n [%]

[$] P values calculated using independent means two sample t-test

7.6   Discussion

7.6.1   Strengths & limitations

There was a high response rate from this population based survey (70.1%). However similar high response rates have been reported from postal surveys of women in similar age ranges (Porter et al., 1996; 51-57, Ballard, 2002; 45-60, Brazier et al., 2005). Porter et al. (1996) used a postal questionnaires obtained a response rate of 72.6% from women aged 45 – 54 (1/3 of these non responders were telephoned to obtain further data which increased the response rate to 76.2%). Ballard (2002) reported a 66% response rate to a postal questionnaire to women aged 51-57 regarding HRT; this survey used two reminders. Brazier et al. (2005) reported a response rate of 72.7% from his survey of 1,080 women aged 45-60.

However, there are limitations to the survey. Women were identified and contacted through GP practice lists, thus any inaccuracies in these lists will have reduced the response rate. Those who respond to surveys are often those for whom the study has the greatest saliency (Edwards et al., 2002). If responders were more likely to be those who have had more symptoms, then the reported 57% prevalence rate of hot flushes in the survey will be higher than the actual prevalence rate for the study population. The survey findings may also be biased against women from more deprived areas (fewer women responded from GP practices in the more deprived areas as measured by the IMD) and illiterate and non English speaking patients. There was some item non-response bias in that not all responders filled in all questions, the impact of this was that some figures will not be representative of the true picture e.g. 64 ticked 'yes' to currently taking HRT, yet only 32 reported the type of HRT taken.

7.6.2   Prevalence and severity of hot flushes

This survey conducted in Sheffield in 2005 has produced up-to-date information on the prevalence and severity of hot flushes and other symptoms of the menopause in the local female population. 51.6% (442/865) of responders reported experiencing hot flushes. Other population based surveys in the UK population of women in the same age range have reported similar findings. An unpublished survey of 702 women aged 45 to 65, recruited through GP practices conducted in Sheffield (Zoellner, 2002) in late 2000, found that 58% of women had hot flushes (mean age of responders was 52.8). The largest UK population based survey (8,000 women) was conducted in the Grampian area of Scotland in 1996 (Porter et al. 1996) reported that 57% of women aged 45-54 were experiencing hot flushes. 22% of respondents to the UK Grampian survey reported that hot flushes were a problem compared to the Sheffield 2005 finding of 29%. One possible cause of the higher Sheffield figure is that there was a

markedly lower percentage of HRT users reported in the Sheffield 2005 survey (7.5%) compared to the 19% reported in the Grampian survey.

7.6.3   Types of treatments used

This survey has gathered information on the types of treatments used by women to help with their menopausal hot flushes. 64/856 (7.5%) women reported currently taking HRT; this figure may be an underestimate as 5% (n=6) of women who reported that they took medication did not then bother to fill in details of the medication that they were taking. If we assume that all 6 women were taking HRT then the maximum number of women who were taking HRT would be 70/856 (8.2%). This adjusted figure is similar to the 10% figure found in an analysis of HRT use in women aged 50 and over in the UK General Practice Research Database (Watson et al., 2006) which reported that prevalence of HRT use had fallen from 17% in 2002 to 10% in 2004. Significantly higher estimates of HRT use had been reported by the Million Women study collaborators (2003) (33%), a Sheffield population based survey (Zoellner, 2002) which found that 32% of responders were then current users of HRT, and an earlier survey of 8,000 women conducted in the Grampian region of Scotland (Porter et al., 1996) which found that 19% of responders (aged 45 – 54) were taking HRT.

7.6.4   Women's attitudes towards HRT and their experiences of HRT

The survey has produced up-to-date information on women's attitudes towards HRT and their experiences of HRT. A third of responders had taken HRT with 43.3% having taken it for five years or more. 43.8% of users were women who had had a hysterectomy. 61% of women reported having experienced side effects, 39.3% reported stopping due to concerns about the risks or long term side effects of HRT, and 32.2% reported having stopped due to side effects or health problems from HRT.

7.6.5   A possible 'Hot Flush' Cohort

The survey has identified a number of women suitable for the possible 'Hot Flush' Cohort (Table 7.7). From sending out self completed postal questionnaires to 1,200 women aged 45 - 64, 131/856 women were identified as having an unmet need and therefore were suitable for inclusion in the proposed 'Hot Flush' Cohort. These women all reported having 14 or more hot flushes a week at the time of the survey and were willing to fill in a further questionnaire. 40% (53/131) described their hot flushes as severe or very severe. Their mean and median age was 54 and the majority of women were post menopausal (78/125) and 6/131 were currently taking HRT and 59/131 were ex HRT users. They were similar to the population of all responders in terms of age and medication but were dissimilar in terms of hot flushes and night sweats, menopausal status, previous use of HRT and side effects from HRT and IMD score.

7.7   Summary

7.7.1   Scoping information

This survey has produced up-to-date information on the prevalence and severity of hot flushes and other symptoms of the menopause in the local female population

This survey has also gathered information on the wide variety of types of treatments used by women to help with their menopausal hot flushes (treatment as usual). With over 49 different types of 'menopause medications' reported, there was no clear type of treatment that should be a comparator intervention in the proposed trial. In what had been the most popular treatment for menopausal hot flushes – HRT – this survey reported a marked decline in the percentage of women taking HRT compared to previous surveys, despite a slightly higher than average medication use[41]. 71.5% of women reported that they had stopped HRT either due to side effects/health problems from HRT or concern about the long term risks/side effects rather than because they did not need it any more. These are women who may consider a non HRT treatment for their hot flushes.

There appears to be an unmet need for a treatment for hot flushes that is both effective and safe in the short and long term. With regards to possible RCTs of treatments for hot flushes as well as homeopathy, there are a large number of possible comparators including evening primrose oil, soya isoflavones, and a plethora of herbal remedies.

7.7.2   Overall conclusion

This survey has identified both a significant unmet need (women with hot flushes who cannot or do not want to take HRT) and a possible 'Hot Flush' cohort of women with frequent hot flushes. The next chapter takes this scoping information and the possible 'Hot Flush' cohort provided by the survey and designs a pilot study of a 'Hot flush' Patient Cohort RCT with a trial of treatment by a homeopath.

---

[41] The overall prescribed medication mean use (1.64) was slightly higher than that reported by the Health Survey for England reports which reported a mean of 1.3 prescribed medications for all women aged 16 years or over (Health survey for England http://www.archive.official-documents.co.uk/document/doh/survey99/hse99-t11-13.htm accessed 7.4.08).

Chapter 8

A pilot study of the 'Patient Cohort' RCT design

8.1 Introduction

The question this thesis addresses is: *"What type of clinical trial design can provide the information needed to make decisions about the provision of homeopathy in a publicly funded healthcare system?"* Chapter 6 described one such possible appropriate trial design - the 'Patient Cohort' RCT design. The rationale for this particular study design was developed in chapters 2 -5. Chapter 7 reported on the preliminary work needed in order to pilot the design; scoping for the pilot trial and the identification of potential patients for the Hot flush cohort. This chapter describes a small scale preliminary test of the 'Patient Cohort' RCT design applied to the question: *"What is an appropriate RCT design to test the effectiveness of treatment by a homeopath for menopausal hot flushes?"*

This small scale preliminary test of the design could also be described as a pilot study or a feasibility study. The US National Library of Medicine National Institutes of Health Medical Subject Heading (MeSH) defines pilot studies as: *"Small-scale tests of methods and procedures to be used on a larger scale if the pilot study demonstrates that these methods and procedures can work"* and feasibility studies as: *"Studies to determine the advantages or disadvantages, practicability, or capability of accomplishing a projected plan, study, or project"* (http://www.nlm.nih.gov/mesh/MBrowser.html accessed 1.8.08) For ease of reference this small scale preliminary test of the design will be described as a pilot study.

8.1.1 Aim of the pilot study

The aim of the pilot study was to conduct a small scale test of the methods and procedures of the 'Patient Cohort' RCT design as a way of addressing the following research question:

"Does a short course of treatment by a homeopath in addition to usual care/self care reduce the frequency or severity of hot flushes, improve quality of life and demonstrate cost effectiveness?"

8.1.2 Objectives of the pilot study

The objectives of the pilot study were to assess the:

- Willingness of patients to fill in questionnaires, consent to further questionnaires and have data used
- Willingness of participants to accept the intervention
- Rate of compliance with the intervention
- Suitability of the outcome measures chosen
- Variance of the outcome variable
- Changes in the health condition in the control group

Estimates of these parameters, especially the variance, will be used to recalculate the sample size to ensure that any full trial has sufficient power.

8.1.3 Study design

In order to test the clinical and cost effectiveness of treatment by a homeopath, the 'Patient Cohort' RCT design as described in chapter 6 was used. Box 8.1 provides the definition of the design.

Box 8.1   The 'Patient Cohort' RCT design

> **The 'Patient Cohort' RCT design consists of an observational Cohort of patients with the condition of interest, within which multiple RCTs are embedded.**
> - **For each RCT, eligible patients are identified, a proportion of whom are then randomly selected to be offered the intervention.**
> - **The outcomes of the selected eligible patients are compared to the outcomes of the non-randomly selected eligible patients.**
> - **Patient information and consent replicate the processes of routine healthcare wherever possible.**

The proposed intervention in this pilot study is treatment by a homeopath. One implication of the 'Patient Cohort' RCT design is that in order to make the information congruent with that given in usual care (Key Criteria V-VII: Replicate processes of routine healthcare, 'Patient' appropriate information & 'Patient' appropriate consent), no information about the test intervention can be given prior to random selection. Therefore random selection has to take place before it is known whether patients actually want to have the treatment, thus the trial is a trial of the Offer of treatment vs No Offer, rather than a trial of treatment vs no treatment.

In this pilot study the condition of interest was menopausal hot flushes, thus the observational cohort of patients with the condition of interest (Patient Cohort) was a Cohort of patients with menopausal hot flushes ('Hot Flush' Patient Cohort). This pilot study conducted just one pilot trial of treatment by a homeopath but this design allows for multiple trials to be conducted with patients recruited from the Patient Cohort. The study design is depicted in Diagram 8.1 below.

Diagram 8.1   **Pilot study design**
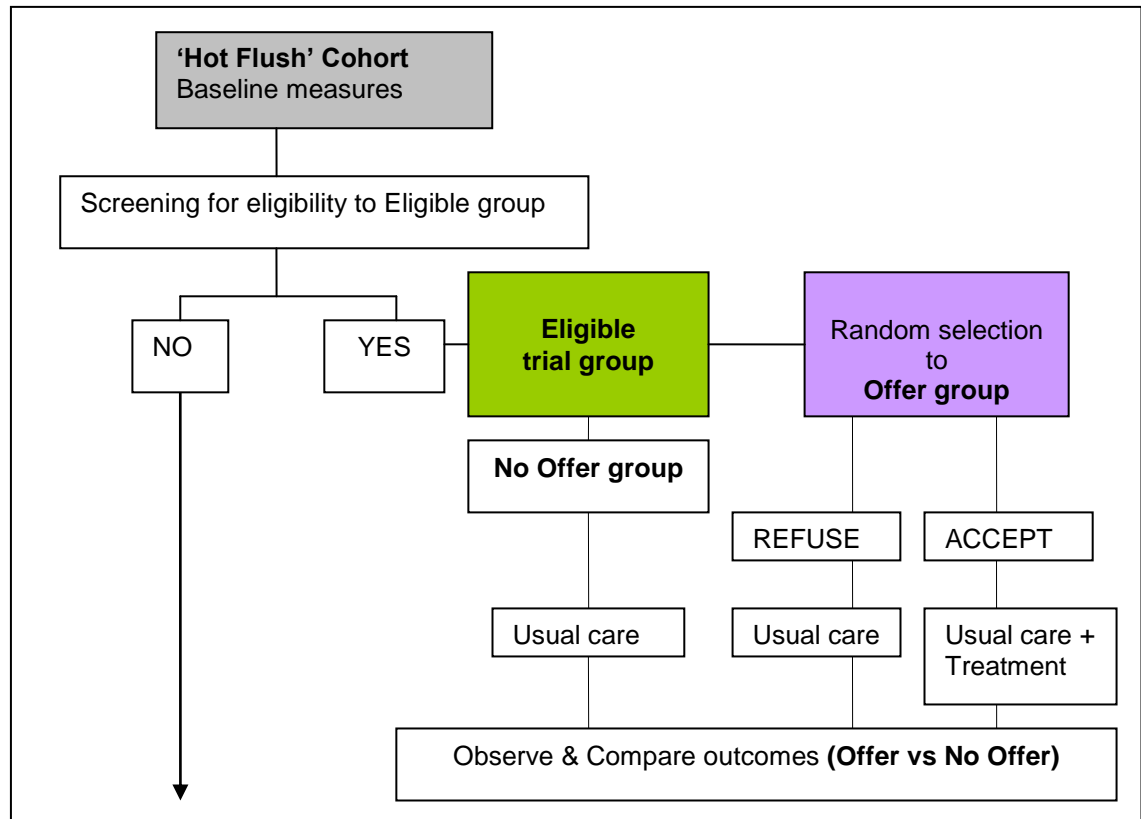
A staged design

As can be seen from Diagram 8.1 there were several stages in the 'Patient Cohort' RCT design:

- Identifying the 'Hot Flush' Patient Cohort
- Screening of the 'Hot Flush' Patient Cohort for eligibility to try treatment ('Eligible' trial group)
- Random selection of a proportion of the 'Eligible' trial group to the Offer group
- Offer of the intervention to patients in the Offer group
- Delivery of the intervention to accepters in the Offer group
- Data collection & comparison of outcomes from all those in the 'Eligible' trial group (the Offer group and the No Offer group).

8.2. Methods

8.2.1 Study design

This study design was a pilot of a 'Patient Cohort' RCT of the clinical and cost effectiveness of treatment by a homeopath for patients with severe and/or frequent menopausal hot flushes.

8.2.2 Institutional & regulatory approvals & funding

The University of Sheffield was the Research governance sponsor (8.9.06) and provided a certificate of clinical trial insurance (Trial number 05/41). The local NHS Sheffield Contraception & Reproduction Research Group consisting of NHS clinicians and both NHS/academic researchers supported the application for the trial to be conducted at the NHS PMS/Menopause clinic at Central Health Clinic in Sheffield at 1 Mulberry Street, Sheffield S1 2PJ. NHS Scientific Review Approval was obtained on 5.9.06 (Consortium ref: ZF89). The UK Medicines Health Regulatory Authority (MHRA) deemed the trial was not a Clinical Trial of an Investigational Medicinal Product (CTIMP) and therefore did not require MHRA Clinical Trials Authorisation. The protocol was submitted to North Sheffield NHS Research Ethics Committee on 5.8.06. (REC ref 06/q2308/131) but rejected on 11.9.06. The study protocol was revised and submitted to South Sheffield NHS Research Ethics Committee on 27.10.06 and approved on 30.1.07 (REC ref 06/Q2305/181). Funding for the trial was from the DH Research Capacity Award of the Principal Investigator (PI). The International Standard Randomised Controlled Trial Number is ISRCTN 02875421.

8.2.3 Settings

The setting for the selection and observation of the 'Hot Flush' Patient Cohort (and 'Eligible' trial group and the Offer group) was six Sheffield NHS GP practices. The setting for the delivery of the intervention (treatment by a homeopath) was the NHS PMS/Menopause clinic, at Central Health Clinic in the Sheffield city centre. Information on the Index of Multiple Deprivation (IMD 2000) scores for the GP practice of each patient was collected in an attempt to acquire patients for the Hot Flush Patient Cohort were balanced with regards to their socio economic status. Each patient was sent a questionnaire that was coded with an individual number.

8.2.4 Patients: Identification and selection

This section describes the identification and the selection of patients for the Hot Flush 'Patient Cohort', the 'Eligible' trial group and the Offer Group and the inclusion and exclusion criteria.

The 'Hot Flush' Patient Cohort

Patients aged 45 - 64 were identified and selected to the Hot Flush Patient Cohort through a series of postal questionnaires sent out between October 2005 and February 2007 (Table 8.1). The results of this first questionnaire (WMHQ1, Appendix D) were reported in Chapter 7. Responders to this first questionnaire were screened and those who reported experiencing 14 or more hot flushes a week and who were willing to receive a further questionnaire became the

'possible' Hot Flush cohort. The characteristics of this 'possible' Hot Flush cohort were described in chapter 7. Patients in this 'possible Hot Flush cohort' were sent a further questionnaire (WMHQ2, Appendix E) in order to obtain baseline measures for the trial. However, by the time the various institutional approvals for the pilot trial had been obtained, 11 months had elapsed. Menopausal hot flushes last on average 2 years thus 11 months later many of the women in the 'possible' Hot Flush cohort would not be experiencing 14 or more hot flushes a week and thus would now not be eligible for the trial of treatment by a homeopath. Once all the institutional approvals had been obtained a further questionnaire (WMHQ3, Appendix F) was sent out to responders to WMHQ2 in order to (1) identify patients who were still experiencing14+ hot flushes, (2) obtain baseline data for the trial, and (3) gain the information needed in order to screen patients for their eligibility for the 'Eligible' trial group. All responders to WMHQ3 became members of the actual 'Hot Flush' Patient Cohort.

Table 8.1   Women's midlife health questionnaires (WMHQs) 1 – 4

Title	Purpose	Sent	Responders
WMHQ1 (Oct/Nov 2005)	Identify issues & options Identify women potentially eligible for the Hot Flush cohort	1,214	856
WMHQ2 (May 2006)	Identification of patients with 14+ hot flushes per week Hot Flush Cohort baseline measures	132	83
WMHQ3 (Feb/March 2007)	Identification of patients with 14+ hot flushes per week Repeat of Hot Flush cohort baseline measures Screening to identify 'Eligible' trial group	82	**70 'Hot Flush' Cohort**
WMHQ4 (Dec 2007)	'Eligible' trial group final outcome measures	**48 'Eligible' trial group**	45

The 'Eligible' trial group

There were 70 patients in the actual 'Hot Flush' Cohort (all responders to WMHQ3). The 'Hot Flush' Cohort was then screened in order to identify patients who were eligible for the trial of treatment by a homeopath ('Eligible' trial group). WMHQ3 (Appendix F) contained the outcome measures for the trial as well as questions which related to the trial inclusion & exclusion criteria. The 'Eligible' trial group was identified from the 'Hot Flush' Cohort by applying the following inclusion and exclusion criteria.

Inclusion criteria

– Female

– 14+ menopausal hot flushes or night sweats per week

– 45 – 65

- consented to fill in a further questionnaire
- consented for their anonymised data to be used for looking at the benefit of treatments for hot flushes

Exclusion criteria

- taking HRT and not intending to stop, using immuno-suppressant drugs or undergoing chemotherapy, or had homeopathic treatment in the past three months for hormone related problems

The Offer group

A proportion of the "Eligible" trial group were selected at random to the Offer group. Those patients who had been randomly selected to the Offer group were then offered a course of treatment by a homeopath which was delivered to those who accepted the offer.

8.2.5 Patients: Recruiting and consenting

This section describes the recruitment and consenting of patients to the 'Hot Flush' Patient Cohort, the 'Eligible' trial group and the Offer Group. How patients were randomly selected is described in the section 8.2.6.

The 'Hot Flush' Patient Cohort: WMHQ2 contained the question *"Would you be willing to help researchers at the University of Sheffield by answering another health questionnaire?" Please tick yes or no.* Those patients who ticked 'yes' to the above question were sent WMHQ3 (Appendix F).

The 'Eligible' trial group: No information was given regarding the intervention being trialled; however two types of consent were sought. Firstly, consent to supply data for the research was sought and obtained through the following question in WMHQ3 *"Would you be willing to help researchers at the University of Sheffield by answering another health questionnaire?" Please tick yes or no.* In addition patients were asked whether they gave their consent to have their data used in the assessment of the intervention with the following question: *"May we use your anonymised data for looking at the benefit of treatments for hot flushes?" Please tick yes or no.*

The Offer group: To those patients who had been randomly selected to the Offer group the Principal Investigator (PI) sent an Offer of treatment letter (Appendix G), a 'Participant' Information Sheet (Appendix H), a Consent form (Appendix J) and a SAE. The Offer of treatment letter informed each woman that *"You have been selected to be offered a course of treatment with a homeopath for your hot flushes and/or night sweats at the NHS Central Health Clinic at 1 Mulberry Street, Sheffield. The treatment is free and we will reimburse your travel costs to and from the appointments with the homeopath."*
The 'Participant' Information Sheet (Appendix H) told patients that *"You have been chosen because you were randomly sampled from a group of patients who have been helping us with our research by filling in our Women's Midlife Health Questionnaires and have reported*

experiencing either frequent or severe hot flushes or night sweat". The 'Participant' Information Sheet also stated that "*You are being invited to have a course of homeopathic treatment. This will consist of a first consultation with a homeopath who will prescribe you a homeopathic medicine to help you with your hot flushes, menopausal symptoms and general wellbeing. You will have a further four appointments with the same homeopath, who will adjust your treatment to maximise the benefit you obtain from the homeopathic treatment.*"

Several days after the letters were sent, each woman was telephoned by the PI in order to answer any questions they had and to see if they were interested in receiving the treatment.

8.2.6   Random selection & allocation concealment & offer of treatment

This section describes the random selection of patients to the Offer group and the process by which the allocation process was concealed. The issue of blinding of participants and/or practitioners is discussed and the process by which patients were offered treatment is described.

Random selection

A random numbers sheet was generated by the statistician (Dr Jenny Freeman) on a one to one basis using a block randomisation procedure, with blocks of 8. The random numbers were put into 82[42] sealed numbered envelopes. Each questionnaire was screened for eligibility by applying the inclusion and exclusion criteria. Eligible questionnaires were assigned a study number by an independent administrator at the University of Sheffield (Kathryn Paulucy) who was blind to any patient data and blind to whether group A or B was the offer of treatment arm. The numbered envelope corresponding to each woman's study number was then opened by the PI to reveal the group to which they had been assigned.

Blinding/masking

A key feature of the 'Patient Cohort' RCT design is that information is given to patients in a similar manner to that (existing or proposed) in routine healthcare, likewise with consent. Concealing the treatment was thus inappropriate; hence there was no masking of the intervention for either the patients or the homeopaths.

Offer of treatment

Patients randomly selected to group B were then sent a letter offering them a course of treatment by a homeopath (Appendix G), 'Participant' Information Sheet (Appendix H), consent form (Appendix J) and a business reply envelope. Those patients who consented to the offer of treatment were then offered an appointment at Central Health Clinic with one of the two study homeopaths.

8.2.7   The intervention (and control)

The intervention was a short course of treatment by a homeopath which consisted of a maximum of five consultations with a homeopath + homeopathic medicines + advice. The intervention was delivered at the Sheffield NHS Central Health Clinic. Honorary contracts were

---

[42] The number of women sent WMHQ3

obtained for the two study homeopaths and clinic rooms booked for the consultations. The two study homeopaths were fully trained, qualified and registered with either the Faculty of Homeopathy (MFHom) or the Society of Homeopaths (RSHom). The PI was not one of the study homeopaths. All homeopathic medicines used were prepared according to homeopathic pharmacopoeias. The first consultation with the homeopath lasted between 45 – 60 minutes and included the prescription of individualised homeopathic medicine(s) which were either given at the end of the consultation from the onsite homeopathic pharmacy stores or picked up from a private clinic in Sheffield (Wellforce Complementary Medicine Service) where both homeopaths also worked or posted to the patient within one or two days of the consultation. Subsequent appointments were 30 minutes in duration and also included the prescription of individualised homeopathic medicine(s) as needed. Occasionally consultations between the patient and the homeopath took place over the phone and prescriptions sent out as required. Patients started their first consultations between two to nine (26.2.07 to 30.4.07) weeks after baseline outcome measures were collected. The last consultation was one week before the 36-week outcome measures were collected, although some patients had finished their last consultation as much as 23 weeks before the 36-week outcomes were reported (however some patients may have been taking their homeopathic medication right up until the 36-week outcomes were reported).

Concurrent medication/treatment: No changes were required regarding patients existing medication and treatments.

Control: In accordance with the 'Patient Cohort' RCT design, those not randomly selected to the Offer group were not given any information about the intervention or the pilot trial.

8.2.8   Choosing the outcome measures

In order to identify the most suitable outcome measures to be used for the 'Patient Cohort' RCT, a brief review of the literature was conducted in 2005. This review searched the online literature of trials of treatments for hot flushes published between 2000 & 2005. Twenty RCTs were identified which used a wide variety of primary and secondary outcome measures including both subjective as well as objective outcome measures. The results of this review are summarised below.

Primary outcome measures

A.   Objective measures

A small number of trials used objective measures for the primary outcome measure: blood samples of measures of concentrations of isoflavones (Van Patten et al., 2002) and FSH/LH (Knight et al., 1999) and electronic monitoring devices for hot flash measurement instruments based on skin temperature had been used in a few studies with small numbers (Carpenter et al.,1999). However a hot flush studies methodological review (Sloan et al, 2001) states that the consensus among hot flush trialists is that patient's subjective experience and opinion regarding the presence of hot flushes takes precedence over objective measures such as skin temperature readings.

B.   Self reported measures

Almost all trials used self reported outcome measures for the primary outcome measure: the Greene Climacteric Scale (e.g. Green et al., 2007), the Kupperman Menopausal Index (e.g. Jacobs et al., 2005), the Patients' Health Questionnaire (e.g. Williamson et al., 2002), Measure Your Medical Outcome Profile (MYMOP) activity and profile score (e.g. Thompson et al., 2005). The most commonly used self reported primary outcome measures (18/20 trials) were in the form of self report daily diaries which recorded either frequency of hot flushes or frequency & severity of hot flushes. The use of self report diaries for data collection has long been established as a valid approach to obtaining data on subjective phenomena (Sloan et al., 2001) with completion rates averaging over 90%.

Hot flush frequency was the primary outcome measure used in 6 trials (e.g. Penotti et al., 2003) and according to Sloan et al., (2001), hot flush frequency data will account for the majority of variability (60-75%) inherent in recorded treatment outcome variables. However, the majority of trials (12/20) used the Hot Flush Frequency & Severity (HFFS) as their primary outcome measure (Van Patten et al., 2002; Stearns et al., 2003; Loprinzi et al., 2002; Loprinzi et al., 2000; Jacobson et al., 2001; .Quella et al., 2000; Scambia et al., 2001, Speroff et al., 2000; St Germain et al., 2001; Upmalis et al., 2000; Jacobs et al., 2005). The additional data gathered from severity data can measure the effect of a hot flush treatment if it reduces a patient's hot flushes from 14 severe hot flushes a week to 14 mild hot flushes a week. Thus the Hot Flush Frequency & Severity scale produces a score that is more readily interpretable in a clinical context (Sloan et al., 2001) and this was the primary outcome measure chosen for the pilot study.

Secondary outcome measures

There was a very wide variety of secondary outcome measures used in these trials.

A.   Objective measures

These were generally biochemical markers and included: weight, BP, cholesterol, progesterone levels, serum isoflavone concentrations, endometrial thickness, arterial pulsatility (Penotti et al., 2003).

B.   Self reported measures

Most of the secondary outcome measures were self reported: SF 36 (Jacobs et al., 2005), EuroQOL & Beck Depression Inventory (Stearns et al., 2000), Dyadic Adjustment Scale (DAS), General Health Questionnaire (GHQ) (Lam et al., 2004), Hot flush visual analogue scale (Williamson et al., 2002), Menopause specific quality of life (Davis 2001), Sleep disturbance VAS (Sloan et al., 2003), Sheehan disability scale (Stearns et al., 2003), Hospital Anxiety and Depression scale (Thompson et al., 2005), Glasgow Homeopathic Hospital Outcome Scale (Thompson et al., 2005) the Greene Climacteric Scale (Scambia et al., 2001, Stearns et al., 2003, Tice 2003, van de Weijer 2002, Green et al., 2007), and MYMOP (Green et al., 2007).

Eligibility criteria

The most common eligibility criterion for these hot flush trials was 14 hot flushes per week (Stearns et al., 2003, Stearns et al., 2000, Loprinzi et al., 2002, Loprinzi et al., 2000). Other

eligibility criteria used were: menopausal symptoms in peri-menopausal patients (St Germain et al., 2001), patients aged 45-59 (Green et al., 2007), postmenopausal patients i.e. 12 months or more of amenorrhea (Van Patten et al., 2002, Stearns et al., 2003, Lam et al., 2004, Davis SR 2001), patients with a history of breast cancer or risk of breast cancer or fear of breast cancer (Van Patten et al., 2002, Stearns et al., 2000, Loprinzi et al., 2002, Loprinzi et al., 2000, Jacobsen et al., 2001), bilateral oopherectomy (Stearns et al., 2003), FSH / Estradiol levels (St Germain et al., 2001, Stearns et al., 2003, Jacobsen et al., 2001), BMI between 20 and 31 (St Germain et al., 2001), stopped HRT at least 6 weeks before screening (Stearns et al., 2003).

8.2.8   Outcome measures chosen: clinical effectiveness

Two types of outcome measures have been chosen to be piloted for the full study – measures of clinical effectiveness and measures of cost effectiveness. The outcome measures chosen to assess the clinical effectiveness of the intervention were the Hot flush Frequency & Severity Score, and the Greene Climacteric Scale and Measure Your Medical Outcome Profile.

Primary outcome measure of clinical effectiveness

The Hot Flush Frequency & Severity Score (HFFSS) (Stearns et al., 2000) was chosen as the primary outcome measure to measure the clinical effectiveness of the homeopathic intervention in treating hot flushes because it was the most commonly used trial primary outcome measure. The description and algorithm for this outcome measure is reported in Sloan et al., (2001) and Loprinzi et al., (2002) and is as follows: The HFFS score is derived from the hot flush diary forms which are filled in daily by patients who record the frequency and severity of every hot flush they experience during one week. Thus the HFFS score = hot flush frequency x hot flush severity (mild = 1, moderate = 2, severe = 3, very severe = 4) which were totalled to give a weekly total score, this weekly total score is then divided by 7 to give the final HFFS score.

Secondary outcome measures of clinical effectiveness

A variety of secondary outcome measures were chosen to assess clinical effectiveness:
The Greene Climacteric Scale (GCS) (Greene, 1998) was chosen as a secondary outcome measure for this pilot as the GCS elicits the type and severity of a broad variety of menopausal symptoms rather than just focussing on vasomotor symptoms. The GCS and its subscales have been used as primary outcome measures in two trials (Lam et al., 2004, Green et al., 2007), and as secondary outcome measures in five trials (Scambia et al., 2001, Stearns et al., 2003, Tice 2003, van de Weijer 2002, Green et al., 2007).
The GCS asks patients to score *'how bothered'* they are by each of 21 menopausal symptoms – *'not at all'* (0) – *'a little'* (1) – *'quite a bit'* (2) – *'extremely'* (3). Greene (1998) does not give any indication as to how the scores should be reported and so there is heterogeneity in the reporting of GCS scores in trials using this outcome measure. If a patient answered all 21 questions then the range of possible scores is 0 – 63 however in the pilot study 6/48 patients did not answer all questions.

The missing data was explored in order to decide how it should be handled. The baseline answers for 17 questions had answers missing (range 1 – 4, median 2, mean 2.24) with no particular question being unanswered more than another. The number of questions answered by those six patients with missing data was 4, 11, 12, 19, 20, & 20 thus 4% (42/1008) of the GCS baseline data was missing.

Various options for handling this missing data were considered. One option was to calculate the total possible score for each patient according to the number of questions they had each answered, but this method makes the assumption that patient's missing scores would be equal to an average of the scores they did actually give. This assumption is unlikely as it is more likely that patients answered the most salient questions and that these questions would have higher scores than the unanswered questions. The strategy adopted to handle the missing data was to carry the last observation forward from the previous questionnaires (WMHQ2 and where necessary WMHQ1), a commonly used method (Green et al., 2007) of handling missing data. However it is recommended that this method should be used with caution.

The 36-week data was also examined and 10/44 questionnaires had missing GCS data. Of these 10 questionnaires, the number of questions answered by each patient was as follows: 5, 6, 6, 9, 10, 15, 15, 16, 19, 20, 20. Thus 9.7% (90/924) of the GCS 36-week data was missing.

Measure Your Medical Outcomes Profile 2 (MYMOP) (Patterson, 1996) is a validated patient generated outcome measure. MYMOP was chosen in an attempt to widen the range of data sources to include the patient's choice for treatment outcomes as well as the researchers' choices. MYMOP consists of four separate questions: Primary symptom, Secondary symptom, Activity, Wellbeing. The Primary symptom score of MYMOP was used to identify the symptom that is most bothering the patient at baseline. The MYMOP Wellbeing score was used to calculate any change in quality of life experienced by the participants in addition to EQ-5D scores

8.2.9   Outcome measures chosen: cost effectiveness

This study piloted the data collection methods used to collect the necessary cost effectiveness data for the full study. In the full study, costs will be measured from both an NHS and a societal perspective. Cost effectiveness will be measured in terms of quality adjusted life years (QALYs) gained. The proposed method of calculating the cost effectiveness of the Offer of the intervention compared to the Non-Offer will be calculated using NHS costs (the direct costs associated with the treatment) and non NHS costs (costs incurred by other public sector budgets, patient travel costs, other out of pocket expenses incurred by the patient, informal care costs, patients time costs incurred while receiving treatment, productivity costs associated with morbidity).

The following outcome measures were chosen to be tested as tools to facilitate the assessment of the cost effectiveness of the intervention:

EQ-5D (Rabin & de Charro, 2001). The EQ-5D Health Questionnaire is a widely used generic measure of health status that provides a simple descriptive profile and a single index value (0-

1) that can be used in the clinical and economic evaluation of health care. EQ-5D asks five questions with regards to the patient's mobility, self-care, usual activities, pain/discomfort, anxiety/depression. EQ-5D is one of the most common measures recommended for use in cost-effectiveness analyses based on QALYs http://www.euroqol.org/ (accessed 30.8.08).

Medication Change

Change in the number of medications being taken by each patient was measured by the Medication Change Questionnaire (MCQ) being developed by Patterson (2004). This questionnaire asks patients to *'list all medications, tablets, ointments, drops and inhalers; both those prescribed by you and those that you buy yourself'* on a daily basis over a 7-day period. The aim of the Medication Change Questionnaire (MCQ) is to monitor all the medication taken over a 7 day period both prescribed and self prescribed.

Patients also filled in 2 A4 pages of answers to the following questions:

Admission to hospital or day unit - whether in the last 3 months they had been admitted to a hospital or day unit. If so, then they were asked to record the length of stay, name of hospital, emergency admission, and reason for admission.

Visits to GP surgery –the number of visits to their GP surgery which could include seeing their GP, nurse, or another healthcare professional at their GP surgery

Visits to other health professional –the number of visits to a consultant, occupational therapist, physiotherapist, nurse practitioner or other; and whether they had paid for the visit.

Travel to GP – how they usually traveled to their GP surgery or other treatment site – walk, taxi, car, public transport, ambulance or other

Days off –how many days off from paid employment they had taken as a result of their hot flushes or night sweats and whether they lost earnings as a result of any days off. Patients were asked if their hot flushes or night sweats had prevented them from carrying out their household tasks or leisure activities.

CAM practitioners – visits to any Complementary & Alternative Medicine (CAM) practitioners during the last month for their hot flushes or night sweats – and if so the number of visits and the cost per visit.

Other conditions - receiving any treatment for any condition other than hot flushes or night sweats and to state the condition.

8.2.10 Follow up

Follow up was at 36-weeks post randomisation by postal questionnaire WMHQ4 (Appendix K). One reminder was sent four weeks after the first WMHQ4. The follow up data covers the period from 36 -40 weeks after baseline.

8.2.11 Sample size

Since this was a pilot and it was not known how many patients would return the questionnaires or meet the inclusion & exclusion criteria, no sample size calculations were made, indeed one of the objectives of this pilot study was to determine initial data for the primary outcome measure in order to perform a sample size calculation for a full trial. For pilot studies, a general

rule of thumb is to take 30 patients or greater to estimate a parameter (Lancaster et al., 2004). A writer (Sloan et al., 2001) on the methodological issues for hot flush trials recommends approximately 50 patients per arm is appropriate for understanding the effect that an intervention has on hot flushes and that *"25 to 30 patients provide a reasonably close estimate to the final results which suggests that this is an appropriate patient number for pilot trials" (Sloan et al., 2001 p.4288).* This information is based on data from 7 placebo controlled trials for a variety of interventions (Vit E, Soy, Clonidine, Venlafaxine, Fluoxetine & Megesterol). From the initial population sample of 1,200 patients, 48 were identified who met the pilot 'Patient Cohort' RCT criteria, thus there were sufficient number of patients to conduct a pilot according to the recommendations of Sloan et al. (2001) and Lancaster et al. (2004).

8.2.12 Ethical issues

Random selection took place before information about the proposed intervention was given to patients and before patient consent to treatment had been requested (similar to trials that use cluster randomisation where GP practices or Health Authorities or Hospitals or days are randomised rather than individual patients). It might be argued that patients not randomly selected to the Offer group could be seen as being denied a form of care that they might have wished to have received. The ethics of clinical trials is complex. In addressing the ethics of this particular trial there are a number of factors to be taken into consideration. Firstly, there was no RCT evidence that treatment by a homeopath improved patient outcomes. Secondly, treatment by a homeopath was available for just two patients a month via the NHS in Sheffield by referral from Central Health Clinic PMS Menopause Service. Thirdly, those patients not randomly selected to the Offer group were not the only patients being denied treatment by a homeopath as it could be argued that all patients aged 45 – 64 in Sheffield were potentially eligible at the start of this study and those patients not selected to the initial observational study (WMHQ1) were also denied the study treatment. The acceptability of this study design (and method of random selection) to all stakeholders in NHS clinical trials still needs to be determined. Ethical issues that relate to the Patient Cohort RCT design are discussed elsewhere in this thesis in chapters 4, 5 and 10.

8.2.13 Data collection

There were two types of data created in the conduct of this trial - Patient reported data and Homeopath reported data. Piloting of data collection forms & questionnaires is important especially when the patient has to self-complete the form (Lancaster et al., 2004).

Patient reported data & questionnaire design

Information on the outcomes of the pilot trial was collected through two postal questionnaires WMHQ3 & WMHQ4 (Appendices F & K), some aspects of the design of these questionnaires have already been discussed in chapter 7. There are however some additional points with regards to WMHQ3 & WMHQ4.

Saliency is the apparent relevance, importance and interest of the questionnaire to the respondent and is a very important influence on response rates (McColl et al., 2001). The title

of all the questionnaires used to obtain data for the pilot (and the scoping study reported in chapter 7) was purposefully broad as it was thought that if questionnaires were entitled 'Hot flush' survey that this might increase saliency bias. General questions tended to precede more specific questions (McColl et al., 2001). Financial incentives improve return rates for questionnaires (McColl et al., 2001; Mapstone et al., 2007) thus in order to maximise return rates (and thus enhancing the validity of the results) financial incentives were used at each stage. WMHQ1 & 2 used for the scoping surveys (chapter 7) and WMHQ3 & 4 used to collect data for the pilot trial all used financial incentives (discussed in 8.4.1).

WMHQ3 & 4 contained many of the same questions as WMHQ1 but did not include the questions on alternative therapist use, physical activity and diet. WMHQ3 & 4 were longer than WMHQ1 & 2 (8 sides rather than 6) as they included all the outcome measures for the trial: EQ-5D, MYMOP, Medication Change Questionnaire, and the Hot flush frequency and severity questionnaire. All data from WMHQ3 & WMHQ4 was inputted into Microsoft Excel spreadsheets and then analysed using SPSS version 12.0 for windows.

Homeopath reported data

The CONsolidated Standards of Reporting Trials (CONSORT) reporting guidelines (www.consort-statement.org) require little or no information about treatments and those who give the treatments and recent reviews of 'homeopathy' trials have highlighted general problems in the conduct (Linde et al., 2001) and design of trials (Bell et al., 2004). Dean (2004) recommended that published reports of 'homeopathy' trials should contain sufficient information on theoretical models, case analysis strategies, pharmacy and prescriptions to aid independent appraisal and replication, and has worked to create a supplement to CONSORT reporting guidelines checklist known as the RedHot guidelines (Dean et al., 2007). This checklist was used prior to the trial to ensure that all relevant information was collected and reported. To collect this data a Homeopaths data form was devised which identified for each patient at each consultation the following information:

- Type of homeopathy: individualised (classical), or formula (single, multi constituent or isopathy)
- Analysis strategy: give minimum five reasons for each initial prescription
- Type of analysis tools: repertory, material medica and/or software used

8.2.14 Planned analysis

Descriptive statistics and a CONSORT type flow diagram (Maher et al., 2001) have been used to describe the following: selection of patients to the 'Hot Flush' Cohort, the 'Eligible' trial group and the Offer group; questionnaire completion, consent to a further questionnaire and consent to have data used; acceptance/refusal of the intervention and compliance with the intervention including the number of consultations attended; completion rates of the clinical outcome measures and economic resource data questions; cost of the intervention.

The following patient characteristics reported at baseline are described for all patients (the 'Eligible' trial group and for the Offer and the No Offer group: age, menopausal status, IMD Band, HFFS score, GCS total score, GCS vasomotor score, MYMOP primary symptom 1 & 2

scores, MYMOP Wellbeing score, Number of prescribed/self prescribed medications, Medication total, HRT use & HRT side effects.

It is thought that the analysis of pilot studies should be mainly descriptive or focus on confidence interval estimation (Lancaster et al., 2004) and it is argued that hypothesis testing is not valid if no formal power calculations have been carried out as with such small numbers there is likely to be imbalance in pre-randomisation covariates which would need adjustment in the analysis (Lancaster et al., 2004). However some preliminary exploratory analyses have been conducted; the rationale for this is that this was a stand alone study (Lancaster et al., 2004) and the number of patients although small was as large as or larger than other reported trials. For example, Green et al. (2007) reported the results of 45 women, and 4/21 trials included in the Cochrane systematic review of oral HRT for hot flushes (MacLennan et al., 2002) reported the results of RCTs of 20 – 48 women. Thus some exploratory analyses were conducted, but results from this hypothesis testing should be treated as preliminary and interpreted with caution (Lancaster et al., 2004).

The baseline data was explored to understand the predictive power of each prognostic variable to assess its ability to predict the primary outcome measure (HFFS score at 36-weeks) using the analysis of covariance (using the General Linear Model univariate procedure in SPSS). Further exploratory analyses were conducted of the characteristics of accepters (of the offer of treatment) compared to refusers using the independent two sample t-test for normally distributed metric data and the Mann Whitney U test for non-parametric data. Pearson chi-squared test was used to compare the proportions across a number of categories.

In addition to the above Intention to Treat analyses, Complier Average Causal Effect[43] analysis (CACE) (Hewitt et al., 2006) was used in order to estimate the effect of the treatment on those who accept the offer of treatment. CACE analysis rests on the premise that within the limits of chance, random selection ensures that, on average the proportion of compliers/accepters in the control group is the same as that in the treatment group. CACE analysis then compares the compliers/accepters in the treatment group with the assumed compliers/accepters in the control group calculated by assuming that any non-compliers/accepters in the control group would have the outcomes as non-compliers/accepters in the offer group. Thus CACE analysis measures the average causal effect for the subpopulation of compliers/accepters and preserves the benefits of the initial randomisation.

---

[43] Also known as 'instrumental variable approach (Torgerson & Torgerson, 2008)

8.3   Results

8.3.1   Selection of patients
The selection and consent of patients to the 'Hot Flush' Cohort, the 'Eligible' trial group and the Offer group of the 'Patient Cohort' RCT design is reported in this section and in the Consort type Diagram 8.2.

Hot flush Cohort: Selection to the final 'Hot Flush' Cohort was through a series of three postal questionnaires. WMHQ1 identified 132 patients with hot flushes, WMHQ2 identified 82/132 patients with hot flushes and WMHQ3 identified 70/82 patients with hot flushes – these 70 patients then became the 'Hot Flush' Cohort for the pilot study.

'Eligible' trial group: The Hot flush Cohort was comprised those patients who had returned completed questionnaires WMHQ1, 2 & 3 and who consented to a further questionnaire (70/82). The eligibility criteria for the 'Eligible' trial group were applied easily and quickly from the data contained in WMHQ3. From the Hot flush Cohort 48/70 patients met the 'Eligible' trial group inclusion and exclusion criteria and thus were eligible for the offer of treatment. In total 22/70 patients of the Hot flush cohort did not meet the trial inclusion and exclusion criteria. Reasons for exclusion were: reporting less than 14 hot flushes per week (12/22), on HRT and does not want to stop (5/22), taking immunosuppressant drugs (2/22), not filled in WMHQ3 sufficiently (2/22), already having homeopathic treatment (1/22).

Offer Group: From the 48 patients in the 'Eligible' trial group, half (24/48) were then randomly selected to be offered the treatment (the 'Offer' group). This pilot used 1:1 randomisation[44] in order to gain the maximum amount of power from the data. One woman telephoned to say that she was unsure if her hot flushes were due to the menopause or her rheumatoid arthritis and thus was she eligible – she was told yes. Those patients in the 'No Offer' group were not contacted or given any information regarding the trial and the offer of treatment.

8.3.2   Willingness of patients to fill in questionnaires
The majority of patients were willing to fill in questionnaires (Table 8.2). Full baseline data was available for the 'Eligible' trial group (as completed & returned WMHQ3 was a criterion of 'Eligible' trial group inclusion). However the 36-week data was incomplete as 45/48 (93.8%) returned completed WMHQ4. All 4/48 (8.3%) patients who failed to return their WMHQ4 were in the 'Offer' group of which 3 had refused the offer of treatment and 1 had accepted.

---

[44] In the full 'Patient Cohort' RCT design it is likely that randomisation will be unequal i.e. 4:1 rather than equal 1:1 as in this pilot. It is anticipated that the design will enable larger numbers of patients to be recruited to the 'Eligible' trial group than with standard RCT procedures for recruitment.

Table 8.2   **Willingness to fill in questionnaires**

Questionnaire	Date	Sent	Returned	Response rate
WMHQ3 Baseline	Feb 2007	83	70	84.3%
WMHQ4 36-weeks	Dec 2007	48	45	93.8%

Recruitment to the observational cohort was through rolling information and consent with patients at the end of each questionnaire being asked if they *'Would help us by filling in another health questionnaire in the future?'* (Table 8.3)

8.3.3   Willingness of patients to consent to have data used (rates of uptake & attrition)

Patients at the end of each questionnaire were asked *'May we use your anonymised data for looking at the benefit of treatments for hot flushes?'* This question was inserted in the questionnaire in order to address the issue of patient data being used for the purposes of the clinical trial even though the patient had not been informed about the trial (and thus had not consented to participate in the trial). Almost all patients who responded (97.7% n=43/44) gave permission to have their *'anonymised data used for looking at the benefit of treatments for hot flushes'* (Table 8.3).

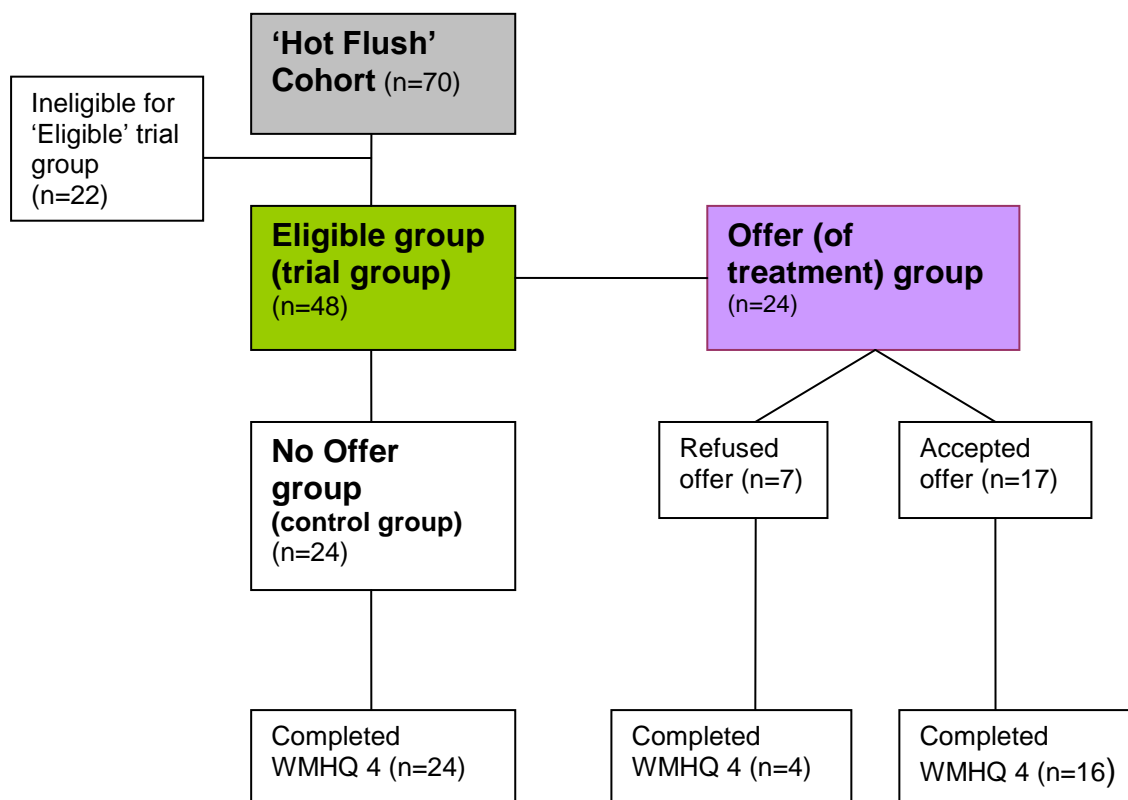**Table 8.3**   **Willingness to have data used and fill in further questionnaires**

Questionnaire	Willingness to have data used	Willingness further questionnaire
WMHQ3	Yes 47/48	Yes 48/48
WMHQ4	Yes 43/44	Yes 43/44

However one patient (in the No Offer group) refused permission in both WMHQ3 & 4. This patient's 36-week data was removed but baseline data for this patient was included; the rationale for this being that baseline data could not in itself provide an assessment of benefit of the treatment being trialled.

8.3.4   Willingness to accept the intervention

Information relating to the Offer group is reported in the Consort type Diagram 8.2. The Offer group can be divided into two subgroups: accepters and refusers.

Diagram 8.2   **Flow of patients in pilot 'Patient Cohort' RCT**

'Hot Flush' Cohort (n=70)

Ineligible for 'Eligible' trial group (n=22)

Eligible group (trial group) (n=48)

Offer (of treatment) group (n=24)

No Offer group (control group) (n=24)

Refused offer (n=7)

Accepted offer (n=17)

Completed WMHQ 4 (n=24)

Completed WMHQ 4 (n=4)

Completed WMHQ 4 (n=16)

17/24 (70.8%) patients accepted the offer of treatment (accepters) and 7/24 (29.2%) refused the offer of treatment (refusers). Reasons for refusal were: moved out of Sheffield (1), already seeing GP & hospital (1), not got enough time (1), no hot flushes (1), depressed & too difficult to get to clinic (1), not applicable to me – too many other health problems (1), initially accepted then refused due to 'health reasons after discussion with husband' (1).

Patients who accepted the offer of treatment signed and returned their Consent forms and booked their first appointment at the NHS Central Health Clinic for a consultation with one of the two study homeopaths.

8.3.5   Intervention: Consultations & homeopathic remedies

Consultations with the study homeopaths took place at Central Health Clinic between 26.2.07 and 15.10.07. The seventeen patients received a total of 57 appointments (there were an additionals 8 DNAs - Did not attend appointment). Two patients arrived at the clinic reception but did not manage to locate the homeopath, neither patient returned. The study homeopath familiar with working at Central Health Clinic was not affected by this problem.

The number of appointments that patients attended ranged from one to five (Table 8.4), one patient had three short telephone appointments in addition to four face to face appointments – this patient has been tabled as having a total of five appointments*. There was a considerable variation in the time between each patient's consultations with the study homeopaths (2 to 10 weeks). This is in line with the variation seen in routine practice.

Table 8.4   **Offer group: appointments, accepters and compliers**

Appointments attended	Number of patients	Accepters vs refusers	Compliers vs Non-compliers
0	7	Refusers (n=7)	
1	3		Non-compliers (n=3)
2	1	Accepters (n=17)	Compliers (n=14)
3	4		
4	5		
5	4*		
		Total =24	Total = 17

Homeopaths reported using a total of 18 different homeopathic remedies with the two most commonly prescribed remedies being Sepia (prescribed 15 times) and Lachesis (prescribed 9 times). Some prescriptions were a one-off single dose whereas other prescriptions were taken twice daily every day. The most frequently given advice recorded was to increase water intake (4 patients) and reduce/stop coffee (2). A more detailed analysis of the Homeopath Reported data will be presented to the homeopathy profession. All patients were offered a refund of their travel costs to and from the clinic however in the pilot no patients claimed their travel costs.

8.3.6   Compliance with the intervention

The intervention was a short course of treatment by a homeopath which consisted of up to five consultations with a homeopath + homeopathic medicines + advice. The number of consultations varied according to the wishes of the patient and/or homeopath. The only information available on compliance from the pilot was the number of consultations that took place. There was no formal measuring of whether patients actually took the homeopathic medicines prescribed or followed the advice given (although these are not commonly met issues in routine homeopathic practice).

Compliance with the intervention: Over two thirds (70.8% 17/24) of patients in the Offer group accepted the offer (Diagram 8.2). Patients who accepted had a mean of 3.29 appointments and a median of 4 appointments, and only four patients had all five appointments.

Defining compliance: Compliance with the intervention was not defined in the protocol for the pilot. One possible definition of compliance would be a minimum of two consultations with the homeopath (this needs discussion with the homeopaths) which would mean that 14/24 patients could be described as having had complied with the intervention – a short course of treatment by a homeopath i.e. two or more consultations.

153

8.3.7 Completion of the clinical outcome measures

The following information describes the data from those 44/48 patients who returned completed (or almost completed) WMHQ4 during the 36 to 40 week time period (however one patient's data was removed for analysis purposes).

Hot flush frequency & severity: Full completion of this outcome measure was a requirement for 'Eligible' trial group inclusion at baseline. At 36-weeks 42/44 patients completed this outcome measure. Two patients were phoned by the PI to ask them to quantify the number of hot flushes they had had which then brought the total to 44/44.

Greene Climacteric Scale (GCS): At baseline, 87.5% (42/48) of responders answered all 21 questions, and at 36-weeks 73.3% (33/45) of all responders answered all 21 questions. Missing data was imputed by using the last observation carried forward method and has already been discussed in section 8.2.8. The most commonly left out questions were 'loss of interest in most things' & 'heart beating quickly & strongly', 'feeling tense or nervous' and 'excitable'. The most frequently filled in questions were 'hot flushes' & 'feeling tired or lacking in energy'. This issue has been reported by other researchers using this outcome measure (Green et al., 2007).

MYMOP Symptom 1 & 2: This requires patients to choose the two symptoms that bother them the most, to write down the symptoms and then score them on a Likert scale of 0 to 6. At baseline completion rates for MYMOP symptoms 1 & 2 were high with just 3/48 patients leaving symptom 1 blank (6/48 patients left symptom 2 blank and 1/48 patients misinterpreted the instructions putting two scores in for each symptom rather than one). At 36-weeks 3/44 patients did not complete symptoms 1, and 3/44 patients did not complete symptom 2.

MYMOP Wellbeing: The completion rate for the wellbeing question was good with 47/48 patients recording their wellbeing scores at baseline and 42/44 patients completing this question at 36-weeks.

Table 8.5   Completion rates for clinical outcome measures

	Baseline	36-weeks		
Outcome measure	**All patients**	**All patients**	**Offer N=24**	**No offer N=24**
Hot flush frequency severity score	48	44	20 (83%)	24(100%)
Greene Climacteric Scale	48	44	14(58%)	19(79%)
MYMOP Primary symptom	45	41	18(75%)	23(96%)
MYMOP Wellbeing score	47	42	19(79%)	23(96%)
EuroQol-5D	48	42	20(83%)	22(92%)
Economic resource data	48	42	20(83%)	20(83%)

A third of patients (17/45) reported a different symptom 1 at baseline compared to 36-weeks making the interpretation of this data impossible. In retrospect, when WMHQ4 was sent out, the symptoms that patients had reported in WMHQ3 should have been written in WHMQ4 – this would have made the data useable.

EuroQol-5D: All patients successfully completed the EQ-5D outcome measures at baseline. At 36-weeks, of the completed questionnaires 42/45 patients recorded their EQ-5D scores.

Medication change questionnaire: Patients provided a significant amount of detailed data regarding their medication including the name of the medication they were taking, whether it was prescribed for them or self prescribed and how many of each medication they took for each of seven days. It is not known how complete this data is however.

The difference in completion rates between the Offer and No Offer groups is marked (Table 8.5), with all four non completers being in the Offer group and three out of four non completers being treatment refusers (Diagram 8.2). Future research should explore whether this was a chance occurrence or a characteristic of this research method.

8.3.8.   Economic resource data

The feasibility of collecting economic resource data for a full trial was tested in the pilot. The completion rates for the economic resource data were high (Table 8.5). Patients seemed to understand the questions although there was some confusion with regards to whether visits to allied health professionals such as community psychiatric nurses or physiotherapists counted as visits to GP surgery (GP or nurse) or hospital visits.

The economic resource data is reported in terms of A. NHS health service costs (cost of the intervention & general illness costs) and B. Non health service costs. Combining health service & non health service costs will provide a societal perspective on costs. Information on costs is taken from tables in the Personal Social Services Research Unit (PSSRU) Unit costs of social care 2007 (http://www.pssru.ac.uk/uc/uc2007contents.htm accessed 1.9.08).

.A.   NHS health services costs

Homeopathic treatment costs: The two study homeopaths were paid £40 per patient contact hour (the same amount as was charged by homeopaths providing homeopathy at the Sheffield NHS menopause/PMS clinic in 2006). The total number of contact hours it took to treat the 17 patients in the trial was 29.5 hours which equates to 1.74 hours each per patient. The total cost of the homeopaths time was £1,220 (mean £71.76 per patient). The total cost of the homeopathic medicines was £60 (£3.52 per patient). Thus the total treatment cost was £1,280 (£1,220 + £60) which equals £75.29 per patient per course of treatment. A full economic costing would also need to include the cost of the rooms, reception and administration staff.

General illness costs: Data was collected on the number of hospital admissions, visits to GP surgery (GP or nurse), and visits to other health professionals. From an NHS perspective hospital admissions are costly, therefore accurate collection of this data is vital. Patients were asked if they had been admitted to hospital in the previous 3 months, however questions did not distinguish between day case hospital admissions (£129) and in patient hospital admissions (£243). Table 8.6 calculates costs assuming a mean of £186 ((£129 + £243)/ 2). There were 4 hospital admissions in the previous 3 months at baseline and at 36-weeks there were 6 admissions in total reported, 2 in the Offer group (1 day bladder problem, 1 day bladder repair) and 4 in the No Offer group (1 day stroke symptoms, 1 day gall bladder removed, 1 day sharp pain under shoulder and 1 day but reason not stated).

Table 8.6   Health service costs data at 36-weeks

	'Eligible' trial patients	Offer group	Total cost	No Offer group	Total cost
Hospital admissions @ £186 each	6 admissions (by 5 patients)	2/20	£372	4/24	£744
Visits to GP surgery @ £22 each	49 visits (by 25 patients)	13/20	£286	36/24	£792
Visits to other health professionals @ £43 each	28 visits (by 12 patients)	11/20	£473	17/24	£731
Total costs			**£1,131**		**£2,267**

Visits to GP surgeries

This question included visits to GP, nurse at GP surgery, Community Psychiatric Nurse, nurse, herbalist & Chronic Fatigue Syndrome clinic (community based). Over half (25/44) of patients reported having visited their GP in the previous three months, with 49 visits to GP surgeries by 25 patients (Table 8.6). The PSSRU costs visits to GPs as £22 per visit.

Visits to other health professionals

Over a quarter (12/44) of patients had reported visits to other health professionals. This included visits to (or from) consultants, occupational therapists, physiotherapist, nurse practitioner and others (chiropractor, hydrotherapy). The PSSRU has a range of costs for other health professionals ranging from £23 for a district nurse to £63 for a home visit from physiotherapist. Table 8.6 assumes a mean of £43 per visit ((£23 + £63)/2 = £43).

The pilot data shows the NHS health service costs for the Offer group were £1,131(Table 8.6) + £1,220 (treatment by a homeopath) + £60 (cost of homeopathic remedies) = £2,411 compared to £2,267 (general illness costs Table 8.6) for the No Offer group.

B.   Non health service costs

Data on the following items were collected: patient travel costs, time taken off work, loss of earnings, and impact of hot flushes/night sweats on household activities/leisure activities in terms of days. Table 8.7 reports the non health service costs data at 36-weeks. 40/44 women reported that they did not work but 2/4 patients reported taking time off work as a result of their hot flushes. 6/44 patients reported that their hot flushes impacted on their household tasks and 4/44 reported an impact on their leisure activities with the impact ranging from 1 day to 'all the time'.

Table 8.7   Non health service costs data at 36-weeks

	'Eligible' trial patients	Offer group Total per person	No Offer group
Time taken off work	2 patients	3 days	10 days
Loss of earnings	0 patients		
Impact on household activities	7 patients	20 days, 3 days, 3 days, 5 days.	15 days, nearly every day, 6 days
Impact on leisure activities	7 patients	4 days, 7 days, 3 days, 6 days	6 days, 10 days, nearly every day,

The Office for National Statistics annual survey of hours and earning cites the national average wage as £109.96 per day. This figure could be used to calculate the economic cost of time off work, loss of earnings, and impact on household & leisure activities in the full trial.

8.3.9   Baseline characteristics: All patients

The baseline characteristics of the 'Eligible' trial group, the Offer group and the No Offer group are reported in Table 8.8. The 'Eligible' trial group consisted of 48 patients with a mean age of 54.7 years (range 46 to 64) the majority of whom were menopausal (no menses in the last 12 months) or post hysterectomy. At baseline patients reported taking a mean 2.65 prescribed medications (range 0 – 9) and a mean 1.29 self prescribed medications (range 0 – 9). Half of the 'Eligible' trial group (50%) reported that they had used HRT. Of those who had used HRT (24/48) half (12/24) reported one or more side effects from HRT.

The HFFS data for all patients at baseline was non normal (mean 12.44, median 9.36, mode 4.43) and positively skewed (2.25) as was the distribution of hot flush frequency in the general population (Stearns et al., 2001). There were three outliers who were all in the Offer group. The standard deviation (SD) of the HFFS baseline data for all patients was twice that of the No Offer group (12.10 vs 5.74) and the SD of the HFFS baseline for the Offer group was three times the standard deviation of the No Offer group (15.18 vs 5.74). However the 36-week HFFS data was more normally distributed than the baseline HFFS data (mean 7.63, median 6.43, mode 1.71)

and less positively skewed (1.33). Initially the data was not transformed as the tests used for analysis (analysis of covariance using the General Linear Model option in SPSS) tend to be robust to departures from normality (Sullivan & D'Agostino, 2003). However, a large difference was found between the p-values for the HFFS scores using analysis of covariance and the independent means two sample t-test, so an additional test for nonparametric data was used - the Mann-Whitney U test.

Table 8.8   Baseline Characteristics: All patients

Characteristics	All 'Eligible' trial patients	Offer (n=24)	No Offer (n=24)
Age, yrs (as of Nov 2005)	54.7 (4.29)	54.12 (4.4)	55.42 (4.23)
Menopausal status			
Regular menses	1 [2.1%]	0 [0%]	1 [4.2%]
Irregular menses	5 [10.4%]	4 [16.7%]	1 [4.2%]
No menses in last 12 months	32 [66.7%]	16 [66.7%]	16 [66.7%]
Hysterectomy	10 [20.8]	4 [16.7%]	6 [25.0%]
IMD Band			
Low deprivation	17 [35.4%]	10	7
Medium deprivation	15 [31.3%]	6	9
High deprivation	16 [33.3]	8	8
Hot flush frequency severity score	12.44 (12.10)	16.58 (15.18)	8.30 (5.74)
GCS total score (0-63)	22.38 (10.29)	22.21 (11.14)	22.54 (9.61)
MYMOP **Primary symptom score (0-6)**	4.09 (0.97)	4.32 (1.13) N=22	3.87 (0.76) N=23
MYMOP **Wellbeing score (0-6)**	3.22 (1.50)	3.05 (1.59) N=23	3.37 (1.44) N=24
EQ-5D (0-1)	0.73 (0.20)	0.75 (0.22)	0.72 (0.19)
Number of prescribed medications	2.65 (2.35)	2.92 (2.64)	2.64 (2.04)
Number of self prescribed medications	1.29 (1.83)	1.46 (2.09)	1.13 (1.57)
Medication total (MCQ)	3.94 (3.15)	4.38 (3.32)	3.50 (2.96)
HRT ever used (yes)	24 [50%]	11 [45.8%]	13 [54.2%]
HRT side effect any (yes)	12 [25%]	5 [20.8%]	7 ([9.2%]

Data presented as Mean (SD) or n [%]

8.3.10   Baseline characteristics: Offer vs No Offer groups

Apart from the HFFS data, the baseline characteristics of the Offer and the No Offer group were well matched. There were 44 patients with both baseline and 36-week outcome data, thus the

number of patients available for an intention to treat (ITT) analysis was 44/48. No baseline testing was conducted as baseline tests of imbalance are inappropriate unless the investigators suspect that there are problems with randomisation, (Roberts & Torgerson, 1999). For continuous metric data that was normally distributed an independent t sample test was used to test whether or not the difference between the two independent group means was zero. Analysis of proportions used a Pearson chi-squared test.

There were no statistically significant differences between the two groups with regards to any of the possible prognostic characteristics at baseline apart from the HFFS total scores of the two groups (p=0.02). Having recorded 12 baseline characteristics it is possible to find one or two characteristics showing a significant difference purely due to chance although one obvious possible interpretation of the HFFS baseline scores imbalance between the two groups is that the random selection process had not worked. However the random selection was secure (Section 8.2.6).

8.3.11 36-week follow up data

As this was a stand alone study some exploratory analyses were conducted, results from this hypothesis testing should however be treated as preliminary and interpreted with caution (Lancaster et al., 2004). Table 8.9 reports the 36-week outcome data adjusted for baseline value for the two eligible trial subgroups: Offer vs No Offer. Lower scores indicate better health for all outcome measures (HFFS, GCS, MYMOP) apart from EQ-5D where a higher score indicates better health. Overall 36 week outcomes were returned by 44/48 of patients, however one patient's 36 week data was removed as permission '*to have anonymised data used for looking at the benefit of treatments for hot flushes*' was refused, and not all patients filled in all outcome measures. Numbers of patients providing each outcome are stated in Table 8.9. Using an independent means two sample t-test there was a statistically significant difference between the two groups for EQ-5D (p=0.05), all medication (p=0.05), self prescribed medication (p=0.04) and trends for HFFS (p=0.08), GCS total score (p=0.07), prescribed medication (p=0.07) and MYMOP Primary symptom score (p=0.09). There was no significant difference between groups for the MYMOP Primary symptom score (p=0.56).

Analysis of covariance (using the GLM univariate model) can increase the precision of the estimated effect of treatment and can adjust comparisons between groups for imbalances in important prognostic variables between the groups. In this instance analysis of covariance was used to test if there was any difference between the groups, independent of baseline scores. Using analysis of covariance there was a statistically significant difference between the two groups for the GCS total score (p=0.02) and EQ-5D (p=0.04) and self prescribed medication (p=0.05) and there were trends for all medication (p=0.08) and MYMOP Primary symptom score (p=0.13). There was no statistically significant difference between the two groups for the primary outcome (HFFS) (p=0.64), MYMOP Wellbeing score (p=0.87) or prescribed medication (p=0.33).

Table 8.9   **Eligible trial group: 36-week outcome data adjusted for baseline value**

Characteristics	Offer Mean change[†] & SD (Numbers of patients)	No Offer Mean change[†] & SD (Numbers of patients)	Difference in mean change 95% Confidence Interval	P-value (t-test[§])	P-value (Analysis of covariance)
Hot flush frequency severity score	-6.89 (13.7) (n=20)	-1.16 (3.90) (n=23)	-5.73 (-12.31, 0.85)[$]	0.08[#]	0.64
GCS total score (0-63)	-1.95 (7.16) (n=20)	1.83 (6.19) (n=23)	-3.78 (-7.84, 0.28)	0.07	0.02
MYMOP Primary symptom score (0-6)	-0.50 (1.25) (n=18)	0.09 (0.90) (n=23)	-0.59 (-1.26, 0.92)	0.09	0.13
MYMOP Wellbeing score (0-6)	0.05 (1.51) (n=19)	-0.22 (1.48) (n= 23)	0.27 (-0.66, 1.20)	0.56	0.87
EQ-5D (0-1)	0.07 (0.13) (n=20)	-0.03 (0.18) (n=22)	0.10 (-0.00, 0.19)	0.05	0.04
All medication	-0.80 (2.24) (n=20)	0.61 (2.33) (n=23)	-1.41 (-2.82, 0.00)	0.05	0.08
Prescribed medication	1.10 (4.49) (n=20)	1.50 (2.27) (n=23)	-0.40 (-2.51, 1.71)	0.70	0.33
Self prescribed medications	-0.45 (1.15) (n=20)	0.38 (1.41) (n=23)	-0.83 (-1.62, -0.03)	0.04	0.05

[†] Mean of the difference between the 36-week score and the baseline score
[§] P-values calculated using independent means two sample t-test
[#]Equal variances not assumed

There was little difference between the p-values produced by the two tests (independent means two sample t-test and analysis of covariance) for all the outcomes apart from the primary outcome measure (HFFS) where there was a considerable difference between the p-values produced by the two tests. Equal variances could not be assumed for this outcome measure therefore a Mann Whitney non-parametric test was conducted to compare the means between the two groups for this outcome (this test replaces the actual data values by ranks for the calculations).The Mann Whitney test showed no significant difference between the two groups (p=0.21). The three tests on the primary outcome measure produced three different p-values (0.08, 0.21, 0.64). This may be an instance of the fact that with small numbers there is likely to be imbalance in pre-randomisation covariates (Lancaster et al., 2004). Sullivan & D'Agostino (2003) suggest that tests such as analysis of covariance which use the General Linear Model are robust to departures from normality, however this may be one instance where this is not the case.

8.3.13 Accepters vs Refusers

In order to inform future trial design in this area it is important to understand more about the characteristics of those patients who accepted the intervention compared to those who refused. 17/24 patients accepted the offer of the intervention. Baseline characteristics of accepters and refusers are reported in Table 8.10.

Table 8.10   Baseline characteristics (Accepters versus Refusers)

	Accepters (n=17)	Refusers (n=7)	P value
Age, yrs (as of Nov 2005)	54.0 (4.95)	54.4 (2.67)	0.83
Hot flush frequency severity score	14.71 (13.75)	21.12 (18.57)	0.35
Menopausal status			0.09
Regular menses	0 [0%]	0 [0%]	
Irregular menses	3 [17.6%]	1 [14.3%]	
No menses in last 12 months	13 [76.5%]	3 [42.9%]	
Hysterectomy	1 [5.9%]	3 [42.9%]	
IMD Band			0.13
A (Low IMD)	9	1	
B (Medium IMD)	4	2	
C (High IMD)	4	4	
GCS total score	18.24 (9.57)	31.86 (8.82)	0.004
Prescribed medications (nos.)	2.53 (2.96)	3.71 (1.70)	0.44
Self prescribed medications (nos.)	1.53(2.29)	1.43 (1.81)	0.70
Medication total (MCQ)	4.06 (3.38)	5.14 (3.29)	0.55
HRT (ever used)	29.4% (5 women)	85.7% (6 women)	0.12
HRT (any side effect)	11.8% (2 women)	42.9% (3 women)	0.08

Data presented as mean (SD) or n [%]

Using an independent samples t-test it was found that refusers reported significantly higher GCS scores than accepters (p= 0.004). At baseline refusers were also more likely to have had a hysterectomy (chi-squared p= 0.09) and to have reported HRT side effects (chi-squared p=0.08).

8.3.14 CACE analysis

In the intention to treat analyses (section 8.3.12), the effect of the treatment may have been underestimated as 7/24 (29.2%) patients refused the offer of treatment. In order to estimate the effect of the treatment on those who accepted the offer of treatment, CACE analysis method was used. CACE analysis makes two assumptions: (i) that the compliance rate in the control group would be the same as the compliance rate in the treatment group if they were offered the treatment and (ii) that the offer of treatment itself does not affect outcomes. In this pilot it can be said that, within the limits of randomisation, the first assumption was met and it is likely that the second condition was also met[45]. The terms 'accepter' and 'refuser' have been used in preference to the terms 'complier' and 'non complier'. When allocation is to <u>treatment</u> groups then the terms 'complier' and 'non complier' are relevant. However, in this design patients were allocated to <u>Offer/ No Offer</u> groups then the terms 'accepter' and 'refuser' are more relevant.

To apply CACE analysis, a binary clinically useful outcome was required so the primary outcome measure (HFFS 36 week adjusted score) was transformed from a continuous outcome into a binary outcome. Sloan et al., (2001) recommends that a reduction of 8.4 - 10 points in the HFFS score is the minimum clinical useful effect size (using data derived mainly from HRT trials), however this particular trial patient group consisted of patients who were unable or unwilling to take HRT, so a reduction of 5 points might be clinically significant, (see section 8.4.8 for further discussion of effect sizes). Two CACE analyses were performed; in the first CACE analysis, the adjusted 36 week HFFS scores were transformed into two groups: those that reported 10+ points reduction in their adjusted HFFS 36 week outcome and those that did not.

In the Offer group there were 7/24 refusers (Table 8.11), of whom only one patient reported an improvement of 10+ points in their adjusted HFFS score (an event rate of 1/7). Of the 17/24 treatment offer accepters, 4/17 reported an improvement of 10+ points in their adjusted HFFS score (an event rate of 4/17). For members of the No Offer group (the control group) it is not possible to categorize patients based on their actual accepter/refuser behaviour, however, we know that the only 1/24 of the No Offer patients reported 10+ point improvement in their adjusted HFFS scores. If it is assumed that the same proportion of patients (7/24) would be refusers as in the Offer group, then 7 patients would not have taken up the offer of treatment.

---

[45] It is possible however that an unsought phone call from a researcher offering a possible hot flush treatment may affect a patients perception of their symptoms and perhaps trigger improved healthcare behaviours (self care, prescribed or self prescribed healthcare interventions) leading to an improved prognosis. Future studies using this method should explore whether this assumption is correct.

Table 8.11   Comparison of rates of 10+ point improvers among accepters/refusers

	Offer group; n=24		No Offer group; n=24	
	Symbol	HFFS 10+ improvers ÷ n	Symbol	HFFS 10+ improvers ÷ n
Accepters 17/24	A(i)	4/17	A (c)*	0/17
Refusers 7/24	N (i)	1/7	N (c) *	1/7
Overall outcome	T (i)	5/24	T(c)	1/24

    * highlighted figures are hypothetical rather than observed

If we assume that the offer of treatment has no effect on the outcome, then the HFFS 10+ point improver rate among the refusers in the control (No Offer) group would be the same as that of the actual refusers in the intervention (Offer) group (1/7). Thus the number of HFFS 10+ point improvers that could be expected in this group would be 1. The remaining improvers would have occurred among those in the control group who would have complied with the offer had it been extended to them, which in this case is 0. The CACE analysis in Table 8.12 reports the results of comparing the outcomes of actual accepters with those of a similar subgroup of No Offer patients who could be expected to have accepted the offer had it been given to them.

Table 8.12   Relative risks by type of analysis performed

Analysis	Calculation	Data	Relative risk
Intention to treat	T(i)/T(c)	5/24 ÷ 1/24	5.0
Per protocol	A(i)/T(c)	4/17 ÷ 1/24	6.0
Complier average causal effect	A(i)/A(c)	4/17 ÷ 0/17	Not defined

An intention to treat analysis produces a relative risk (r/n) of 5.0 for a 10+ point improvement in the primary outcome, and a per protocol analysis produces a relative risk of 6.0. But as there were no assumed improvers in the No Offer group, no result for the CACE analysis could be defined. However, for a self limiting condition such as menopausal hot flushes it is implausible that there would be no improvers in the No Offer group, thus 'no assumed improvers' is obviously a false prediction. In order to more correctly estimate event rates with small numbers, Nicholl (1989) suggests using $(r + 1)/(n + 2)$ instead of the usual r/n. As this particular analysis has predicted zero events for the 'improvers' in the No Offer hypothetical accepters group, the above algorithm was applied and the number of improvers/number of accepters ratio in the Offer group altered from 4/17 to 5/19 and the (hypothetical) number of improvers/number of accepters ratio in the No Offer group was altered from 0/17 to1/19 (Table 8.13) and relative risks were recalculated.

Table 8.13   Comparison of rates of 10+ point improvers among accepters and refusers (adjusted for small numbers of events)

	Offer group; n=24		No Offer group; n=24	
	Symbol	HFFS 10+ improvers ÷ n	Symbol	HFFS 10+ improvers ÷ n
Accepters 17/24	A(i)	5/19	A (c)*	1/19
Refusers 7/24	N (i)	1/7	N (c) *	1/7
Overall outcome	T (i)	5/24	T(c)	1/24

* highlighted figures are hypothetical

After adjustment for small numbers of events as per Nicholl (1989), (Table 8.14) a comparison of the outcomes of actual accepters with those of a similar subgroup of No Offer patients who could be expected to have accepted the offer had it been given to them, produces a relative risk of 5.2 using CACE analysis, 5.0 using an ITT analysis and 6.5 using a per protocol analysis.

Table 8.14   Relative risks for a 10+ point improvement by type of analysis performed (adjusted for small numbers of events)

Analysis	Calculation	Data	Relative risk
Intention to treat	T(i)/T(c)	5/24 ÷ 1/24	5.0
Per protocol	A(i)/T(c)	5/19 ÷ 1/24	6.5
Complier average causal effect	A(i)/A(c)	5/19 ÷ 1/19	5.2

8.3.15 Further CACE analysis (5+ point reduction)

A second CACE analysis was conducted for which the adjusted 36 week HFFS scores were transformed into two groups: those that reported 5+ points reduction in their adjusted HFFS 36 week outcome and those that did not. In the Offer group 7/17 accepters and 2/7 refusers reported an improvement of 5+ points in their HFFS adjusted 36 week scores (Table 8.15). For the No Offer group, 3/24 reported a 5+ point improvement. If it is assumed that the proportion of refusers (7/24) would be the same in the No Offer group as in the Offer group then the 5+ point improver rate among the hypothetical refusers in No Offer group would be the same as that of the actual refusers in the Offer group (2/7), therefore the remaining improvers would have occurred among the hypothetical accepters in the No Offer group (1/17).

Table 8.15   Comparison of rates of 5+ point improvers among accepters/refusers

	Offer group; n=24		No Offer group; n=24	
	Symbol	HFFS 5+ improvers ÷ n	Symbol	HFFS 5+ improvers ÷ n
Accepters 17/24	A(i)	7/17	A (c)*	1/17

Refusers 7/24	N (i)	2/7	N (c) *	2/7
Overall outcome	T (i)	9/24	T(c)	3/24

* highlighted figures are hypothetical

Table 8.16 reports the relative risk of a 5+ point improvement in HFFS 36 week adjusted scores according to the type of analysis performed. The CACE analysis predicts a much higher relative risk of a 5+ point improvement for treatment accepters (7.0) compared to the Intention to Treat and per protocol analysis estimates (3.0 and 3.4 respectively).

Table 8.16   Relative risks for a 5+ point improvement by type of analysis performed

Analysis	Calculation	Data	Relative risk
Intention to treat	T(i)/T(c)	9/24 ÷ 3/24	3.0
Per protocol	A(i)/T(c)	7/17 ÷ 3/24	3.4
Complier average causal effect	A(i)/A(c)	7/17 ÷ 1/17	7.0

CACE analysis estimates a relative risk of 7.0 for a 5+ point improvement in the HFFS 36 week adjusted scores for treatment offer accepters and a relative risk of 5.2 for a 10+ point improvement.

8.3.14 Adverse events

No adverse events were reported.

8.4   Discussion

8.4.1   Suitability of the data collection methods & recruitment and consent rates

Failure to recruit sufficient numbers is one of the main reasons for abandoning trials early (hence Key Criterion IX Recruit sufficient numbers). Thus it was important to determine the recruitment rate to the three groups in the 'Patient Cohort' RCT design (the Cohort, 'Eligible' trial group, Offer group).

Practice managers & GPs were willing for patients to be randomly selected from their databases and to send out letters inviting patients to fill in the researcher's questionnaire. Table 8.17 describes the two questionnaires used in the scoping survey (WMHQ1 & 2) and the two questionnaires used in the pilot trial (WMHQ3 & 4), the number of reminders, the financial incentive that the patients were offered and the percentage that were returned.

The highest return rates were for questionnaires used in the pilot trial (WMHQ3 & 4) both of which offered patients a £10 M&S voucher for each completed returned questionnaire. The lower return rates were for WMHQ1 & 2 where patients who returned questionnaires were entered into a prize draw for M&S vouchers (and thus were not guaranteed a financial payment). No conclusions as to the actual effectiveness of these types of financial incentives can be drawn from these results as the conditions varied between WMHQ1, 2, 3 & 4. For example, each questionnaire was sent to a slightly different population (only responders to

WMHQ1 & 2 were sent WMHQ3 & 4), WMHQ1 & 2 differed in length from WMHQ 3 & 4 and reminders were sent out for WMHQ1,3 & 4 but not for WMHQ2 etc.

Table 8.17   Table of Questionnaires

Questionnaire	Date sent	Reminders	Financial incentive	Sent	Returned	Response rate
WMHQ1	Nov 2005	1	Free prize draw 10 x £25	1,214	856	70.5%
WMHQ2	May 2006	0	Free prize draw 5 x £25	132	83	62.8%
WMHQ3	Feb 2007	1	£10 for each completed questionnaire	83	70	84.3%
WMHQ4	Dec 2007	1	£10 for each completed questionnaire	48	45	93.7%

Interestingly in answer to the question '*Would you like to receive the M&S £10 voucher?'* at the end of both questionnaires (WMHQ3 & 4), 8.3% (4/48) of patients said '*no*'. This could be interpreted as either a lack of interest in M&S vouchers or that their primary motive in responding to the questionnaire was altruism.

One patient refused to have her data used, thus this data had to be removed from the exploratory analyses reported in table 8.9, thus reducing the strength of the inferences made from the data overall. Further discussion is needed to assess indeed whether this consent needs to be sought as it has been suggested (McColl et al., 2001) that anonymity has not been demonstrated to have consistent effects on the rate or quality of response. If this consent does need to be sought then further research is needed to understand the issues for patients with regards to their data being used comparatively and to assess the rate at which patients will (or not) comply with this request.

8.4.2   Willingness of patients to accept the intervention

As well as ascertaining the recruitment rate to the Cohort it was important to ascertain what will be the consent rate to the intervention in the Offer group (i.e. ratio of accepters to refusers). Treatment by a homeopath may not appeal to all patients, so this pilot sought to determine the acceptability of this particular intervention. Those who refused the offer appeared to have poorer health (higher GCS scores & more prescribed medication) and to have had poorer

menopausal health (more likely to have had HRT & side effects from HRT). Interestingly, section 8.3.4 reported that 5/7 patients cited factors associated with poor health as the reason for refusing the offer of treatment (*'already seeing GP & hospital', 'depressed & too difficult to get to clinic', 'too many other health problems', 'health reasons'*).

Comparison with other pragmatic trials

How does the acceptance rate of 70.4% (17/24) in this pilot compare to other trials? Green et al., (2007) recruited patients through GP databases and reported an acceptance rate to a waiting list control trial of treatment by a herbalist of 100% (45/45). There have been two pragmatic trials of treatment by a homeopath (Relton et al., in press; Owen, 1990), however direct comparison with these trials is difficult due to the differences between the informed consent procedures used. In a trial of treatment by a homeopath for Irritable Bowel Syndrome (Owen, 1990), 23 patients were recruited and all patients completed the trial, however, no information was given on numbers of patients approached or referred to the trial. In a trial of treatment by a homeopath for Fibromyalgia Syndrome (Relton et al., in press) in which potential participants were told that they would be allocated at random to either the treatment group or no treatment 72.3% (47/65) of eligible patients agreed to participate in the trial, a similar figure to the 70.8% (17/24) found in this pilot; of those who consented and were recruited to the trial and were offered treatment 86.9% (20/23) completed the final trial outcomes.

The information collected in this pilot does not enable us to differentiate between patients who did not want *any* treatment for their hot flushes and those who specifically did not want *treatment by a homeopath* for their hot flushes (this data should be collected in any further trials using this design). Thus it is impossible to tell whether the acceptance rate of 70.8% (17/24) was due to the high unmet need amongst this patient group or the high popularity for the intervention or a combination of both. Although comments regarding the treatment were not sought, one patient did make a written comment[46] at the end of WMHQ4:

"I would like to comment on the homeopathic treatment I received (5 appointments) I was very impressed by the help I had. It was good to talk to someone who understood me and treated not just the flushes but all that was happening in my life. I found this made me feel much better about dealing with some difficult personal issues. I believe all patients should be able to access this service. I'm not sure why I have hot flushes – it could be hot drinks, high blood pressure, hormones etc, I found the above approach helpful. Thank you for this opportunity".

8.4.3   Non-compliance with the offer

The issue of Non-compliance is especially important in Randomised Consent Designs such as the 'Patient Cohort' RCT design, as if patients refuse their allocated treatment, they effectively 'cross over' into the opposing group. This cross over will dilute any treatment effect and make it harder to observe a difference using an ITT analysis, thus possibly causing a Type II error (concluding there is no difference when there is). Non-compliance with the offer in this pilot was 29.2% (17/24) which is considerably higher than the 11.6% (38/43) Non-compliance reported in the 'Adapted randomised consent (Zelen) design' trial (Campbell et al., 2005) and higher than the median Non-compliance rate in SRCD trials of 15% reported in the systematic review

---

[46] Four other patients also wrote unsought for comments at the end of WMHQ4 – these all related to their experience of their hot flushes e.g. *'When I have an alchol (stet) drink.. I have more hot flushes also when I get nervous etc I have more'*.

(Schellings et al, 2006) and the mean Non-compliance rate of 13.8%, reported in Adamson et al.'s systematic review (2006).

8.4.4 Compliance with the treatment

14/17 (83.4%) had two more consultations and 4/17 had all five consultations. There are several different possible reasons for this: the homeopathic treatment brought about the desired result after less than five consultations, dissatisfaction with the intervention, or an as yet unknown reason. Knowledge of the acceptance rate, the factors associated with acceptance and the reasons for discontinuation of the treatment will be vital to informing a future full trial of treatment by a homeopath for menopausal hot flushes. Below is a HFFS 36-week adjusted score stem and leaf plot for number of consultations.

Diagram 8.3 Stem and leaf plot of number of consultations and HFFS scores
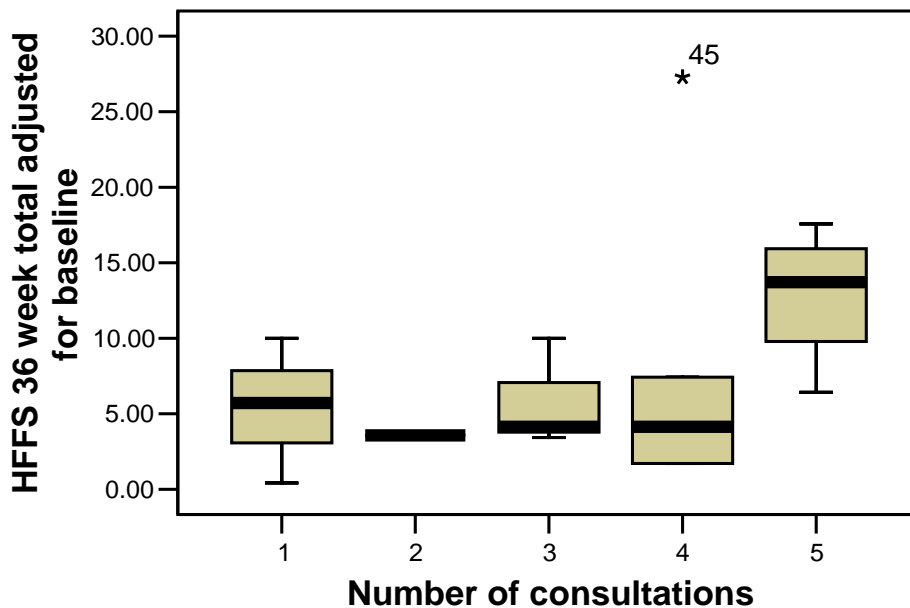
Although patient who had all five consultations reported a mean reduction of around 14 point, using a chi-squared test there was no correlation between the number of consultations and the adjusted HFFS 36-week score.

8.4.5 Suitability of the outcome measures chosen

Completion rates on most questions including the primary outcome measure (HFFS) were generally high apart from the 21-item GCS. GLM univariate analysis of variance demonstrated

that the baseline HFFS score was prognostic of the 36-week score as one would expect of any validated outcome measure (p=0.01). However, the HFFS score gives no measure of the saliency of the vasomotor symptoms.

8.4.6   Variance & SD of the outcome variable

Standard deviation (SD) is a measure of the average distance of all the data values from the mean and variance is the square of the standard deviation. The SD and variance of the HFFS variable were 12.1 & 146.39 at baseline, 5.85 & 34.29 at 36-weeks and 10.1 & 101.25 for 36-weeks adjusted for baseline.

8.4.7   Change in the health condition in the control group
Patients in the control group (No Offer group) at 36-weeks did not report any significant changes in their health with regards to the clinical outcome measures (Table 8.9).

8.4.8   Calculating the sample size
In order to calculate the sample size needed for the full trial the minimum effect size that would be clinically useful needs to be identified. Sloan et al., (2001) recommends that a reduction of 8.4 to 10 points (E[47]) in the HFFS outcome is the minimum size of the effect that would be clinically useful.

This trial population reported a mean baseline HFFS score of 12.44 (Table 8.7) thus a reduction of 10 points would mean an almost complete eradication of the patient's hot flushes. This trial population was recruited from the general population rather than healthy women from clinical settings (Sloan et al., 2001; MacLennan et al., 2002) and thus there may be significant differences that need to be considered when discussing effect sizes, sample sizes.

Fifty per cent of these patients (Table 8.8) were ex-HRT users thus there are several scenarios possible for each patient: taken HRT and it not worked, taken HRT and side effects untenable, or taken HRT but had to stop it due to unacceptable risk factors. In any of these scenarios a reduction of say half the mean baseline HFFS score (6 points) might be clinically significant. It could also be argued that the effect size needs to be reduced even further to take into account the non compliance rate as the greater the non compliance rate then the bigger the risk of a Type II error (concluding that there is no difference when there is). The following section calculates the sample size needed for a full trial for two different effect sizes: a reduction of 10 points and a reduction of 5 points.

Effect size of 10 points mean difference
If we assume that a reduction of 10 points mean difference (E) in the HFFS outcome is the minimum size of the effect that would be clinically useful and a significance level of 0.05, a power of 90% and a SD of the change in the Hot Flush Frequency & Severity Scale for the trial

---

[47] E is the minimum change in the mean which would be clinically useful.

group of 10.06 (Table 8.9), then the following sample size 'rule of thumb' formula (Bowers, 2002 p136) $N = 2 \times SD^2 / E^2 \times k$ can be applied.

$$N = 2 \times 101.20 = 202.41/ 100 = 2.02 \times k (10.5) = 21.25$$

Therefore at least 22 patients would need to be successfully followed up in each group. Although 44 patients were successfully followed up in this pilot, 24 patients in the No Offer group were followed up but only 16 were successfully followed up in the Offer group, thus this pilot was not sufficiently powered to detect a 10 point difference in the means between the two groups.

Effect size of 5 points mean difference

However if one assumes the lower effect size 5 then the sample size needed would be 85 patients per arm.

$$N = 2 \times 101.20 = 202.41/ 25 = 8.1 \times k (10.5) = 85.0$$

Significance levels

Given the scepticism of the intended audience as to effectiveness of the homeopathic remedies (and their low prior probabilities of the effectiveness of treatment by a homeopath) any full trial may well require stronger evidence. In this case then the significance level of 0.01 should perhaps be used[48] which would mean that if E = 10 then the number needed would be 31 per group:

$$N = 2 \times 101.20 = 202.41/ 100 = 2.02 \times k (14.9) = 30.10$$

And if E=5 then 121 patients would need to be successfully followed up in each group:

$$N = 2 \times 101.20 = 202.41/ 25 = 8.1 \times k (14.9) = 120.64$$

Unequal randomisation

These sample size calculations have assumed equal randomisation (1:1). However, the advantage of the 'Patient Cohort' RCT design is that recruitment of large numbers of patients to the Cohort should be easier than with the standard RCT design, and thus the design could use unequal randomisation. For example using unequal randomisation of 4:1, for every five patients in the 'Eligible' trial group, one out of every five patients would be randomly selected to the Offer group

---

[48] For a double blind placebo controlled trial of homeopathic remedies it has been suggested that if there was a positive result for the homeopathic remedy then in order to alter the prior probabilities of those who analyse clinical trials, a significance level of 0.001 or 0.0001 would be needed (Professor Richard Lilford, Foundation for Integrated Health Symposium, Kings Fund, London, November 2007).

This would mean that for an RCT with an expected effect size of 10 points (with 90% power & 0.50 α test significance level), using an unequal randomisation of 4:1 would require a sample size of 70 patients (56:14). And for an RCT with an expected effect size of 5 points (with 90% power & 0.50 α test significance level), then a 4:1 randomisation ratio would require a sample size of 265 patients (212:53).

8.4.9 Three sample sizes

There are in fact three sample sizes that need to be calculated for the full trial: the Hot flush Cohort, the 'Eligible' trial group and the accepter group. The calculation of the sample size for the Hot flush Cohort has already been discussed (Section 8.2.11).

The above sample size calculations (Section 8.4.8) have been discussed with reference to a notional 'trial group' which matches what is described in the 'Patient Cohort' RCT design as the 'Eligible' trial group. Full information prior to consent (as used in standard Informed Consent procedures) weans out those patients who are likely to be non accepters from the final 'trial group', thus in conventional trials the trial group and the accepter group are usually the same. However, in the 'Patient Cohort' RCT design, the 'Eligible' trial group and the accepter group will not be the same as non accepters are not weaned out prior to recruitment to the 'Eligible' trial group. In this pilot, for example, there were 24 in the Offer group, however, 7/24 (29.2%) women refused the offer. The effect of non acceptance rate must be taken into account when calculating sample sizes for Randomised Consent Designs. One way to do this would be to reduce the effect size according to the non acceptance rate, e.g. a predicted 30% non acceptance rate would result in a 30% reduction in the effect size sought.

8.4.10 Database vs treatment seeking patient sample

This version of the 'Patient Cohort' RCT used GP database recruitment & postal questionnaires in order to identify the 'with need' population of women with severe & frequent menopausal hot flushes. This recruitment method was a fast and cheap way of identifying a large number of patients for the Cohort and the 'Eligible' trial group. For a full trial powered to detect an effect size of 10 points (with 90% power & 0.50 α test significance level), then using 4:1 randomisation would require a sample size of 70 patients (56:14). If GP database recruitment and postal questionnaires were used then in order to identify the required sample size (70 patients), 1,750 (70/48 x 1,200) GP database patients would need to be sent postal questionnaires.

With regards to attrition of the Hot flush Cohort using the database selection and postal questionnaires, 93.8% of patients in the 'Eligible' trial group returned their questionnaires at 36-weeks. Further consideration needs to be given to see how attrition rates could be minimised in both the short and long term and individual question completion rates improved. The most

important question to ask about this method of recruitment is whether this method of identifying patients identifies the relevant population for the research question?

8.4.11 Relevance of treatment

The 'Eligible' trial group eventually consisted of patients who had reported having hot flushes in October 2005, although baseline measures were taken in February 2007. The 'Eligible' trial group therefore consisted of women who had been experiencing hot flushes for at least seventeen months.

For patients who are drawn from treatment seeking populations for a particular condition, one would assume an offer of treatment for that condition is likely to be of interest. However the

treatment seeking population is not always the same as the 'with need' population. Patients drawn from a database population may or may not be treatment seeking and it is possible that no treatment seeking patients may either (1) not want treatment or (2) have had standard treatment and it has not worked or (3) have had unacceptable side effects from the treatment or (4) may believe that there is no treatment that can help them. The next two sections discusses the relevance of the offer of treatment from both the patient's and the clinician's perspective.

8.4.12 Relevance of treatment (patient's perspective)

If a woman considers that her joint pain bothers her more than her hot flushes, will an offer of treatment for her hot flushes be of interest or relevance to her? One possible way of assessing the importance of the woman's menopausal hot flushes with regards to her overall health in this pilot study is to examine the patient generated information that was collected using the secondary outcome measure MYMOP.

Table 8.18 lists the symptoms that patients reported as bothering them the most at baseline. The most commonly reported group of symptoms was joint/muscle/back pain. Hot flushes and night sweats was the second most commonly reported group of symptoms with 11/48 patients describing hot flushes or night sweats as either their first symptom (n=9) and/or their second symptom (n=4) symptom that bothered them the most. Of these 11 patients, 8 were randomly selected to the Offer group.

Table 8.18   **Symptoms that bother patients the most at baseline**

MYMOP symptoms that bother patients the most at baseline	Symptom 1 (no. of patients)	Symptom 2 (no. of patients)
Joint/muscle/back pain	11	9
Hot flushes/ night sweats	9	4
Anxiety	4	3
Headaches	3	3
Breathing difficulties	3	1
Insomnia	2	5

Difficulty concentrating	2	1
Palpitations	2	0
Fatigue	2	1
Depression	0	4
Loss of libido	1	3
Other	7	8
Not completed	2	6

Vasomotor symptoms appear to be one of the most important symptoms that bother patients for 12/46 (26%) of the patients recruited and selected to the 'Eligible' trial group. Those patients who reported hot flushes or night sweats as one of the two symptoms that bothered them the

most (patient generated symptoms), reported mean HFFS scores at baseline roughly twice the size of those who did not (Table 8.19). However, the majority of patients 34/46 (73.9%) were most bothered at baseline by other symptoms such as joint/muscle/back pain, anxiety, headaches, breathing difficulties.

Table 8.19   HFFS baseline scores and MYMOP vasomotor symptoms

	MYMOP reported Vasomotor Symptoms	Number of patients	HFFS score at baseline Mean (SD)
HFFS score at baseline	Yes	12	19.4 (14.12)
	No	35	10.3 (10.65)

One would expect that women who reported vasomotor symptoms as bothering them the most, would be more likely to accept an offer of treatment for vasomotor symptoms than those who reported non vasomotor symptoms, as the treatment offer would be more salient. However, in this pilot study, this was not the case. Twelve patients reported hot flushes or night sweats as bothering them the most of whom 8/12 were offered treatment, but 5/8 (62.5%) accepted the offer of treatment. Whereas the 35 women who reported non vasomotor symptoms as bothering them the most, 16/35 were offered treatment and 12/16 (75%) accepted the offer. A chi-squared test using Fisher's exact test was used to assess whether reporting HF or NS as one of the two "symptoms that bother you the most" was prognostic of acceptance/refusal of treatment and there was no evidence that it was (p value 0.65).

Table 8.20   Cross tabulation: patient generated symptoms and offer acceptance

Count		Accepted Offer		Total
		Accepted	Refused	
HF or NS as MYMOP sx1 or 2	yes	5	3	8
	no	12	4	16
Total		17	7	24

But refusers did have lower (i.e. worse) EQ-5D scores, higher (worse) HFFS scores and higher (worse) GCS scores (Table 8.21), a profile not dissimilar to the total refuser group (Table 8.10).

173

Thus although MYMOP symptom 1 & 2 gathered information on the symptoms that bother patients the most, this information does not indicate how likely they are to accept or refuse treatment. But as the numbers here are very low no definite conclusions can be drawn. For an ITT analysis the proportion of those offered the treatment who refuse the offer, can have a significant impact on the analysis. This will be discussed further in the next chapter.

Table 8.21   Refusers and accepters baseline scores

	Accepters Mean (SD)	Refusers Mean (SD)
EQ-5D Index	0.79 (0.28) (n=5)	0.62 (0.15) (n=3)
HFFS baseline	14.20 (7.70) (n=5)	40.52 (5.22) (n=5)
GCS total baseline	13.60 (5.86) (n=5)	35.67 (4.73) (n=3)

8.4.13   Relevance of treatment (clinician's perspective)

Some treatments are very specific in terms of the symptoms/diseases that they target whereas others have a much broader action. For example, HRT has been seen as a treatment not just for menopausal hot flushes but also for a wide variety of other symptoms such as menopausal depression, joint aches and pains, low libido etc. Homeopaths like GPs are generalists rather than specialists (e.g. menopause clinicians) and are taught to adapt their treatment to whatever is the most distressing or most limiting for the patient, with a strong focus on the patient's perspective. Therefore if a patient in a trial of hot flushes presented at the first appointment with non vasomotor symptoms, then the homeopath would treat the woman for her presenting complaint regardless of what the condition being trialled.

8.4.15   Comparison with other hot flush trials

This section compares the pilot trial baseline scores and treatment effects to the results reported by Green et al., (2007), Sloan et al., (2001) and MacLennan et al. (2002). Green et al. reported the results of a recent trial of treatment of menopausal symptoms by a herbal practitioner which used the GCS as a primary outcome. Sloan et al., used HFFS outcomes and reported seven trials of the effectiveness of a variety of pharmaceutical interventions for hot flushes, and MacLennan et al. reported hot flush frequency outcomes (but not Hot Flush Frequency and Severity Scores) and report the results of a Cochrane review of 21 placebo RCTs of oral HRT.

Green et al. (2007) recruited eligible patients through a GP database search of patients aged 46-59 (which screened out those receiving the contraceptive pill or HRT) who were then randomly allocated to waiting list or immediate treatment. Treatment consisted of a course of individualised treatment of six consultations over 5 months, which included discussion of nutrition, lifestyle and individualised herbal prescription. The trials reported by MacLennan et

al., (2002) and Sloan et al., (2001) recruited patients from clinical settings (predominantly menopause clinics) rather than GP databases. The mean age of the pilot 'Patient Cohort' RCT study population was 54 which was similar to Green et al., (2007) but older than the mean age of 50 reported in MacLennan et al., (2002).

Baseline outcome measure scores

Baseline mean HFFS scores for this pilot were 12.44 (SD 12.10) which is within the range reported by Sloan et al., (2001) in his review of seven trials with means of 11.7 – 20.1 per day (SD 7.8 – 15.5) with a median of 14.1. Baseline HFFS scores were not reported in the Cochrane review (MacLennan et al., 2002), and Green et al. (2007) did not use the HFFS outcome measure.

Baseline mean GCS total scores for this pilot were 22.38 (SD 10.29). Green et al., report similar baseline GCS means scores of 20.57 (SD 9.86) for the treatment group and 22.34 (SD10.32) for the control group.

Treatment effects

The average effect of treatments reported in Sloan et al. (2001) was a reduction of 25 to 50% of the HFFS baseline score at 4 weeks.

To calculate the treatment effect found in this pilot study the adjusted HFFS scores for the No Offer group (-1.16) was subtracted from the adjusted HFFS scores of the Offer group (-6.89) to give a reduction of 5.73. As a percentage of the baseline score (12.44) a reduction of 5.73 equates to 46%[49] - a reduction comparable to that reported by Sloan et al. Sloan et al., (2001) state that a 45% reduction in hot flash activity among 25 patients would be required in order to further study a particular drug.

Green et al.'s (2007) pilot trial of treatment by a herbalist for menopausal hot flushes reported a reduction of 8.56 in the GCS total score (which equates to a 42% reduction in baseline GCS total scores), however this pilot reported a lower reduction of 3.78 (which equates to only a 17% reduction in baseline GCS total scores).

8.5   Summary

This small scale test of the methods and procedures found that patients were easily recruited to the Hot flush Cohort and patients for the 'Eligible' trial group were easily identified by applying the trial inclusion/exclusion criteria to the questionnaire data. The questionnaire completion rate for the 'Eligible' trial group at 36-weeks was high (93.7%) and almost all (47/48) patients consented to have their data used. The acceptance rate to the offer of treatment in the Offer

---

[49] The Cochrane systematic review of oral HRT (MacLennan et al.,, 2002) reported a 77% reduction in hot flush frequency (rather than Hot flush frequency & severity HFFS) outcomes for HRT compared to placebo.

group was 70.8% (thus a non acceptance rate of 29.2%); the impact of this acceptance rate on any ITT analysis in the full trial needs further consideration.

Homeopaths were able to deliver the intervention, although unfamiliarity with the clinic reception procedures was associated with two patients prematurely stopping treatment. Patients attended a mean of 3.35 appointments each and 15/17 had two or more appointments. Completion of the outcome measures at 36-weeks was good overall and the primary outcome measure appeared to be acceptable to almost all patients (95% completion rate of the HFFS at 36-weeks which increased to 100% after two telephone calls to patients). The GCS outcome measure had the lowest completion rate at 36-weeks with 73.3% (33/45) of patients filling in all 21 questions. Economic resource data on health service and non health service costs was completed well although there was some confusion as to the exact location of visits to non GP health professionals.

At baseline accepters reported better health than refusers and baseline GCS scores were predictive of whether a patient accepted treatment. The variance of the outcome variable (HFFS) at baseline was 149.39 at baseline but just 34.29 at 36-weeks (the size of the variance has implications for the sample size calculations for the full trial). Apart from more hospital attendances in the control group (5 vs 2), there were no changes in the health condition in the control group with regards to the clinical outcome measures.

An ITT analysis demonstrated no difference between the Offer group and the No Offer group in the primary outcome measure. Despite the trial being underpowered and a 70.8% acceptance rate to the offer of treatment - there was a statistically significant difference between the groups for some of the secondary outcome measures when the data was analysed using analysis of covariance (GCS total score p=0.02, EQ-5D scores p = 0.04 and self prescribed medication p=0.05) with better scores reported by the Offer group. CACE analysis estimated a relative risk of 7.0 for a 5+ point improvement in the HFFS 36 week adjusted scores for treatment offer accepters and a relative risk of 5.2 for a 10+ point improvement. However as multiple tests were conducted it would be inappropriate to place undue significance on these results as they may be chance findings.

This pilot study has provided information that will help reduce uncertainty in the planning of the full trial thus improving the likelihood of the full study being successful. Issues raised in this pilot concerning the 'Patient Cohort' RCT design are discussed in more detail in the next two chapters.

Chapter 9

Evaluation of the pilot of the 'Patient Cohort' RCT design

9.1   Introduction

This thesis has been concerned with '*what works'* and '*solutions to problems'* (Patton, 1990) and has taken an essentially pragmatic approach to the research question. *"What type of clinical trial design can provide the information needed to make decisions about the provision of homeopathy in a publicly funded healthcare system?"* The underlying premise of this thesis has been that in order for a clinical trial to 'work', the design must be appropriate to the perspectives of the stakeholders in that clinical trial. Chapter 8 reported the results of a pilot 'Patient Cohort' RCT of treatment for hot flushes by a homeopath with reference to the proposed full study. This chapter now turns to evaluating the 'Patient Cohort' RCT design as a research tool *per se,* using information derived from the pilot to evaluate the design i.e. did the pilot of the 'Patient Cohort' RCT design work?.

9.1.1   Evaluation
Evaluation has been defined as '*a process that attempts to determine as systematically and objectively as possible the relevance, effectiveness and impact of activities in the light of their*

objectives...' (Last, 2001). This evaluation is concerned with the *'activities'* of the pilot 'Patient Cohort' RCT reported in chapter 8. The possible *'objectives'* of this evaluation however are multiple and require elucidation.

9.1.2   Objectives of the evaluation

The explicit objectives of the pilot were to assess the feasibility of accomplishing a projected plan of the methods used in the trial design, e.g. the willingness of patients to fill in questionnaires, in order to inform the design of the full study. These objectives have already been evaluated in Chapter 8 with reference to the proposed full study and published as a brief conference report (MacPherson et al., 2008).

Turning to the clinical trial design *per se,* the most obvious objective would be to evaluate how well the activities of the pilot met the twelve key criteria for appropriate clinical trial design identified in chapters 2 – 5. Since this thesis suggests that the 'Patient Cohort' RCT design is capable of meeting all twelve key criteria, this type of evaluation would be quite pertinent.

A *post hoc* evaluation of the pilot with regards to the twelve key criteria was attempted; however, for a variety of reasons, little useful information was derived. As there was no planned evaluation of the design itself, there were no standards for deciding whether the criteria had been met. An additional difficulty was that many criteria overlapped with each other (see section 6.1.3); this overlapping, although a form of corroboration of the importance of each criterion, became a source of confusion during the *post hoc* evaluation.

The evaluation using the twelve key criteria has not been reported here, instead, an evaluation with an objective more congruent with the aim of this thesis was identified, that of evaluating how well the pilot of the 'Patient Cohort' RCT design 'worked'. The objective in the mind of the PI when constructing the 'Patient Cohort' RCT design was to *"design a clinical trial that …. would reflect real world clinical practice as I understood it" (1.6.3),* a pragmatic trial that would provide a basis for decisions about healthcare (Last, 2001) within an NHS setting. Thus the evaluation in this chapter focuses on this objective, and evaluates the pilot of the design with regards to its pragmatic qualities. This is a retrospective evaluation of a pilot of part of the 'Patient Cohort' RCT design and not the full design.

9.1.3   Aims & objectives

The aim of this chapter is to evaluate the pilot of the 'Patient Cohort' RCT design. The objectives of this chapter are to:

- Identify the best tool(s) for assessing the pragmatic purpose of the design
- Apply the best tool(s) to assess the pragmatic purpose of the design

9.1.4   Terminology

Before commencing the evaluation, issues with the terminology used needs to be addressed.

The key criteria evolved from a literature where the norm is to use standard Informed Consent procedures, and where 'recruitment' into a trial in practice means that 'prospective trial participants' (i.e. patients) have been given multiple types of information and agreed to multiple

consents all at a single time point. In reporting the 'Patient Cohort' RCT design new terms had to be developed (e.g. Eligible trial group) in order to describe multi stage recruitment process used in the design: recruitment to the observational Cohort, recruitment to the Eligible trial

group, recruitment to the Offer group. Thus depending on the design referred to the term 'recruitment' has different meanings.

9.2 Evaluation tools

The aim of this section is to identify the most appropriate tool(s) for assessing the pragmatic qualities of the pilot of the design.

The quality of a trial is a complex concept (Jadad & Enkin, 2007) but there are tools which attempt to assess the quality of trials. A variety of tools were identified through literature searches and discussions with colleagues. Two types of tool were identified: the first type of tool attempts to assess the internal or external validity of a trial (Jadad et al., 1996; Downs & Black, 1998; Rothwell, 2005) and the second type of tool attempts to assess the purpose of the trial (Gartlehner et al., 2006; Thorpe et al., 2009).

9.2.1 Tools for assessing trials: internal and external validity

Currently, by far the most widely used and cited tool for measuring trial quality is the 5- item JADAD scale (Jadad et al., 1996) which measures internal validity i.e. the degree to which the trial design, conduct, analysis and presentation have minimized or avoided biased comparisons of the interventions being analysed (Jadad & Enkin, 2007 p.49). This scale contains five items measuring the simple components of internal validity. Table 9.1 lists the questions and scorings and then assesses the internal validity of the pilot 'Patient Cohort' RCT of treatment by a homeopath as measured by the Jadad scale.

Table 9.1   **JADAD Scale to assess trial quality**

JADAD Questions	Pilot Patient Cohort RCT	Points
1. Was the study described as randomized?	YES	1
2. Was the study described as double-blind?	NO	0
3. Was there a description of withdrawals?	YES	1
Give a score of 1 point for each 'yes' or 0 points for each 'no'		
Give 1 additional point each if randomization/blinding (methods) appropriate	Randomization methods reported and appropriate	1
Deduct 1 point each if randomization/blinding		0

inappropriate		
Total		3/5

The pilot scored 3/5 points on the JADAD Scale, the maximum possible for an unblinded/ pragmatic trial[50]. The design does not fully 'work' according the to the JADAD scale and systematic reviews will report trials using the 'Patient Cohort' RCT design as having (at the most) 'medium' rather than high internal validity. Jadad & Enkin (2007) acknowledge the narrow scope of the JADAD scale as a tool to assess trial quality and suggest that there should be separate assessments of components related to other aspects of trial quality such as external validity.

There are two tools which measure external validity, both of which are in the form of lengthy checklists (Rothwell, 2005; Downs & Black, 1998). Rothwell (2005) has constructed a 39-item checklist of items that potentially affect external validity and Downs & Black's 26-item checklist (designed for the assessment of the quality of both randomised and non-randomised studies) includes items that relate to external as well as internal validity. These tools are rarely used.

9.2.2   Tools for assessing trials: effectiveness vs efficacy trials

The second type of tool for assessing trials assesses the purpose of a trial i.e. does the trial ask whether an intervention can work under (tightly controlled) ideal conditions (explanatory or efficacy trial) or does it ask whether an intervention can work under the usual conditions that apply where it would be used (effectiveness or pragmatic trial)?

There are two tools that address the purpose of a trial (Gartlehner et al., 2006; Thorpe et al., 2009). The first tool attempts to distinguish effectiveness from efficacy trials in systematic reviews of drug trials. This tool was published in a technical review by the US Agency for Healthcare Research and Quality (AHRQ) (Gartlehner et al., 2006) and uses seven criteria (Table 9.2).

Table 9.2   Gartlehner et al.'s criteria

1	Populations in primary care
2	Less stringent eligibility criteria
3	Health outcomes Quality of Life
4	Long study duration & clinically relevant treatment modalities
5	Assessment of adverse events
6	Adequate sample size to assess a minimally important

---

[50] Placebos and blinding of patient or practitioner are not used in routine healthcare therefore they can have no place in a pragmatic trial.

	difference from the patient perspective
7	Intention to treat analysis

In developing this tool the directors of seven US and Canadian Evidence Based Centers were asked to nominate 4 trials that exemplified pragmatic trials and 2 trials that exemplified explanatory trials, after which two blinded raters applied the 7 criteria and decided yes/no for

each trial. The views of the directors of the Evidence Practice Center as to what constituted an 'effectiveness study' differed greatly. Testing the seven criteria found that a cut-off of six criteria produced a specificity of 0.83 and a sensitivity of 0.72 (Gartlehner et al., 2006). Although this tool helps increase the chances of guessing correctly, it does not accurately distinguish between effectiveness and efficacy trials[51].

9.3   The PRECIS evaluation tool

An international consortium promoting pragmatic trials in health care in low and middle income countries (PRACTiHC http://www.practihc.org/) has worked on the basis of two premises. Firstly, that the pragmatic or explanatory purpose of a trial is better expressed as a continuum rather than as an either/or dichotomy, and secondly, that individual components of a trial often vary in their 'pragmaticness'. This consortium has developed a tool that aims to help triallists assess the degree to which design decisions align with the trial's stated purpose along a pragmatic versus explanatory continuum for 10 domains - the PRagmatic-Explanatory Continuum Indicator Summary (PRECIS). The aim of this tool is to help research funders, ethics committees, trial registers and journal editors, assess whether a trial's design matches the needs of those who will use the results. As the 'Patient Cohort' RCT design has a pragmatic purpose, the most suitable tool for evaluating the pragmatic purpose of the design is the PRECIS tool. This section evaluates whether the 'Patient Cohort' RCT design worked using the PRECIS tool with reference to the activities of the pilot. This tool is due to be published in 2009[52] and the lead author (Assistant professor K.E.Thorpe, Department of Public Health Sciences, University of Toronto) has given permission for the tool to be discussed in this thesis.

---

51 The pilot of the 'Patient Cohort' RCT design met six out of seven of the criteria, but not the criterion 6, as the sample size was not adequate to assess a minimally important difference from the patient perspective; however, a main study of this design would meet all seven criteria. The pilot of the design works with regards to Gartlehner's tool as it would correctly guess that the design was an effectiveness trial.

52 A power point presentation of an earlier version of the PRECIS design is available at http://www.unicem-web.org/support/precis.ppt#1 (accessed 5.12.08)

9.3.1 The PRECIS tool

Thorpe et al. argue that triallists need to make design decisions in ten domains that determine the extent to which a trial is explanatory or pragmatic and that pragmatic RCTs address these ten domains in different ways when there are important differences between usual and ideal circumstances. The PRECIS tool consists of ten lines arranged like the spokes of a wheel, with the explanatory pole near the hub and the pragmatic pole on the rim (Diagram 9.1).

Diagram 9.1   Blank PRECIS wheel
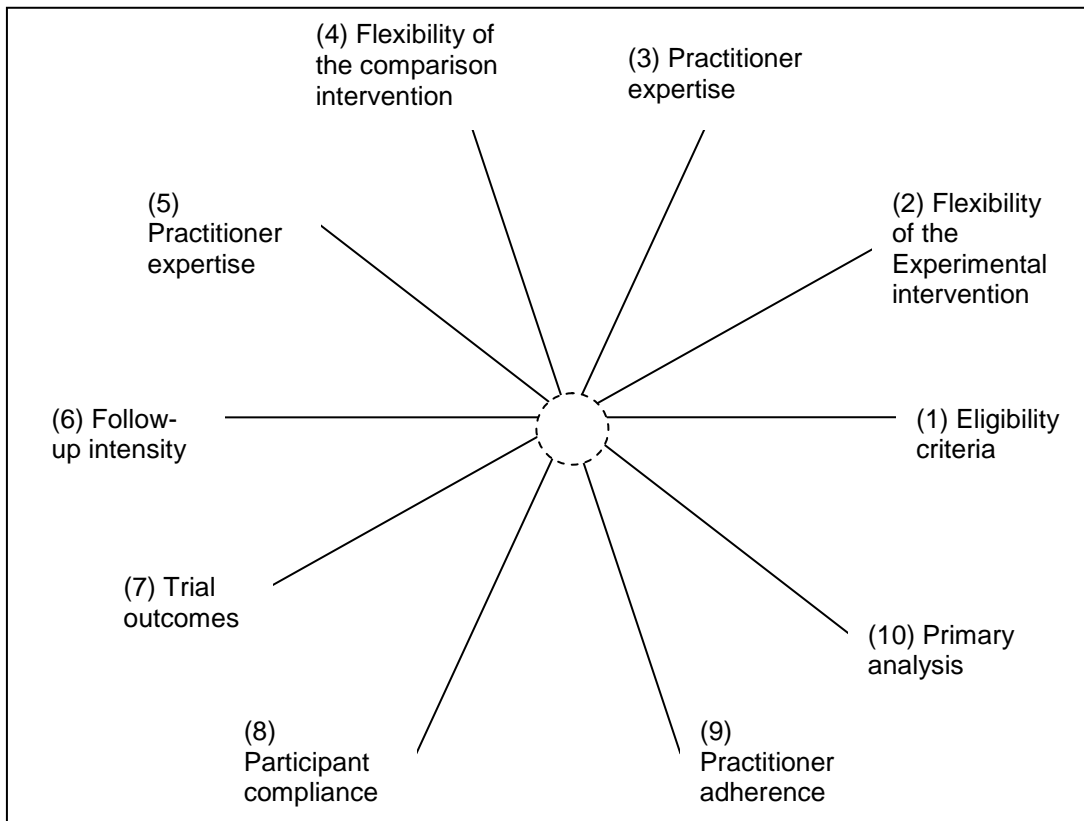
The tool depicts whether a trial is tending to be narrowly focussed (near the hub) i.e. asking whether an intervention can work under ideal circumstances, or tending to take a broad view (near the rim) –i.e. asking whether an intervention works under usual conditions. The ten domains in the PRECIS tool are listed in Table 9.3.

Table 9.3   PRECIS domains

1	Eligibility criteria for study participants
2	Flexibility with which the experimental intervention is applied
3	Degree of practitioner expertise in applying and monitoring the experimental intervention
4	Flexibility with which the comparison intervention(s) is applied
5	Degree of practitioner expertise in applying/ monitoring comparison intervention(s)

6	Intensity of follow-up of trial participants
7	Nature of measured outcomes
8	Intensity of measuring participants' compliance with the prescribed intervention, and whether compliance-improving strategies are employed
9	Intensity of measuring collaborators' adherence to the study protocol, and whether adherence-improving strategies are employed
10	Specification and scope of the primary analysis

9.3.2 Applying the PRECIS tool to the pilot of the 'Patient Cohort' RCT design

This section briefly describes the pragmatic pole of each domain (in italics) and then the pilot of the 'Patient Cohort' RCT design is assessed (by the author) with regards to each domain. Diagram 9.2 plots the pilot of the 'Patient Cohort' RCT design on the spokes of the PRECIS tool.

1. Eligibility criteria for study participants

The most extreme pragmatic approach to eligibility would place as few restrictions on the study population as possible and identify study participants with the condition of interest from as many sources as possible.

The design took a pragmatic approach to eligibility. Eligibility criteria for the Cohort population were kept purposefully broad (female, 14+ menopausal hot flushes or night sweats per week, aged 45 – 65, consented to fill in a further questionnaire and for their anonymised data to be used to look for the benefit of treatments for hot flushes). This is in contrast to some hot flush RCTs with more restrictive exclusion criteria e.g. women with severe hot flushes (MacLennan et al., 2002). The eligibility criteria for the 'Eligible' trial group were slightly more restrictive as three extra exclusion criteria were added (taking HRT and not intending to stop, using immuno-suppressant drugs or undergoing chemotherapy, or had homeopathic treatment in the past three months for hormone related problems). These exclusion criteria were added in order to reflect usual practice as patients in these categories would not be expected to receive the intervention.

The Hot Flush Cohort population, from which the Eligible trial group were selected, consisted of responders to a series of three questionnaires sent out to a sample of women registered with 6 GP practices in Sheffield. The majority of 'Hot flush' RCTs recruit patients from clinical settings such as menopause clinics rather than GP populations (MacLennan et al., 2002). As the possible sources from which the population for the main study could be selected could be further broadened to include women from every GP practice in Sheffield, or the UK, the pilot was plotted near the edge of the pragmatic pole of the Eligibility criteria domain.

2. Experimental intervention flexibility

The pragmatic approach leaves the details of how to implement the experimental intervention up to the practitioners. Additionally, the pragmatic approach would not dictate which co-interventions were permitted or how to deliver them.

In the pilot the experimental intervention was defined broadly as 'treatment by a homeopath' which was further defined as *'a short course of treatment by a homeopath which consisted of up to five consultations with a homeopath + homeopathic medicines + advice'*. A more explanatory approach would have detailed the style of prescribing used by the homeopaths e.g. individualised (Thompson et al. 2005), or the types of homeopathic medicines that they could use e.g. *Lachesis* (Gautier, 1987), or even the particular potencies or repetitions of the

homeopathic medicines e.g. *Lachesis 30c* once a week. The pilot of the design was plotted at the pragmatic pole of the Experimental intervention flexibility domain.

3.   Experimental intervention practitioner expertise

A pragmatic approach would put the experimental intervention into the hands of all practitioners treating study participants. In the pilot the two study homeopaths chosen were fully trained, qualified and registered. The pilot was plotted 2/3rds of the way towards the pragmatic pole as practitioners were chosen who had the most experience in working with this patient group in Sheffield. One of the practitioners is widely regarded as an expert in this area.

4.   Comparison intervention flexibility

A pragmatic trial would compare an intervention to usual practice or the best available alternative management strategy whereas an explanatory trial would restrict the flexibility of the comparison intervention and might use placebo. In the pilot the comparator was the 'No Offer' group who were a 'usual care' group. In accordance with the 'Patient Cohort' RCT design, those not randomly selected to the Offer group were not given any information about the intervention or the pilot trial, and thus they continued with their usual care (which may have included no care) uncontaminated by any information as to any treatments being trialled. Given the total comparison intervention flexibility, the pilot of the design was plotted at the pragmatic rim of this domain.

5.   Comparison Intervention practitioner expertise

A pragmatic approach would not restrict comparison intervention practitioners but instead aim to identify the benefits and harms of the intervention in comparison with usual practice in the settings of interest. In the pilot there was no restriction in any of the interventions that the patients received or self prescribed in the comparator group (the 'No Offer' group). Given the total comparison intervention practitioner expertise flexibility, the pilot of the design was plotted at the pragmatic rim of this domain.

6.   Follow-up intensity

A pragmatic approach would not seek follow-up contact with the study participants in excess of the usual practices for the practitioner. It could go even further to have no contact with study

participants and obtain outcome data by other means instead. In the pilot study we must distinguish between follow-up appointments for treatment and follow-up to obtain outcome data. In the pilot, the number and frequency of follow-up visits were not pre-specified and thus were not more or less frequent than would typically occur outside a trial. Follow-up to obtain outcome data for the study was by postal questionnaire at 36 weeks post randomisation with one reminder sent out after four weeks. A more pragmatic design might have obtained data without directly contacting patients i.e. from routine data, and thus the pilot was plotted near the end of the pragmatic pole of the Follow-up intensity domain.

7.   Trial outcomes

A pragmatic approach would use short and long term outcomes of direct importance to the study participants whereas an explanatory approach would consider only outcomes know to be directly acted upon by the experimental intervention. An explanatory approach to the design would have used objective measures such as blood samples of measures of Follicle Stimulating Hormone (Knight et al., 1999) or electronic monitoring devices for hot flush measurement instruments based on skin temperature (Carpenter et al., 1999). In this pilot, no surrogate or objective markers were used. Instead, a variety of outcomes were used all of which were subjectively reported by the patients and which required no special training of tests. Outcomes most obviously of direct importance to the study participants were EQ-5D a quality of life outcome and MYMOP, a patient generated outcome measure which asked patients which two symptoms bothered them the most, thus prioritising the patient's perspective on their health and wellbeing. However outcomes were used which were of interest to the NHS but not necessarily the patient – e.g. economic resource data. No long term outcomes were collected and thus the pilot was plotted 2/3rds of the way towards the pragmatic end of the Trial outcomes domain pole.

8.   Participant compliance with 'prescribed' intervention
The pragmatic approach recognises that non-compliance with any intervention is a reality. Since any measurement of compliance has the possibility of altering compliance, the pragmatic approach in a trial would be not to measure or use compliance information in any way. Compliance with the intervention would be measured (indirectly) purely for descriptive purposes at the conclusion of the trial.
In the pilot, compliance with the intervention (in terms of the acceptance or non acceptance of the Offer of treatment and the number of consultations attended by accepters) was measured indirectly and purely for descriptive purposes. Thus the pilot took a very pragmatic approach and was plotted at the pragmatic end of the Participant compliance domain pole.

9.   Practitioner adherence to study protocol
A purely pragmatic approach would not be concerned with how practitioners vary or customise a trial protocol to suit their setting, whereas an explanatory approach would apply adherence

improving strategies to practitioners with documented poor adherence. The pilot trial was conducted in just one setting and limited information regarding the behaviour of the homeopaths was collected (e.g. homeopathic remedies prescribed and advice given). Practice variability was not a question addressed in this study, and thus this pilot was plotted at the pragmatic of the Practitioner adherence domain.

.

10.   Primary analysis

Assuming other aspects of a trial have been treated in a pragmatic fashion, an analysis that makes no special allowance for non-compliance, non-adherence, practice variability etc is most appropriate for this question. Many hot flush HRT trials have used analyses other than Intention to Treat as their primary analysis (MacLennan et al., 2002). The primary analysis of the pilot

trial was an Intention To Treat (ITT) analysis which made no special allowance for non-compliance with treatment allocation or non-adherence to the treatment provided. This pilot was plotted at the pragmatic end of the Primary analysis domain pole. Unlike standard RCT designs, the multi-stage recruitment process used in the 'Patient Cohort' RCT design does not screen out likely non compliers prior to randomisation, therefore an ITT analysis (one that makes no special allowance for non-compliance or non adherence) runs the risk of a Type II error - concluding that there is no difference when there actually is.

Diagram 9.2   PRECIS summary for the pilot 'Patient Cohort' RCT design
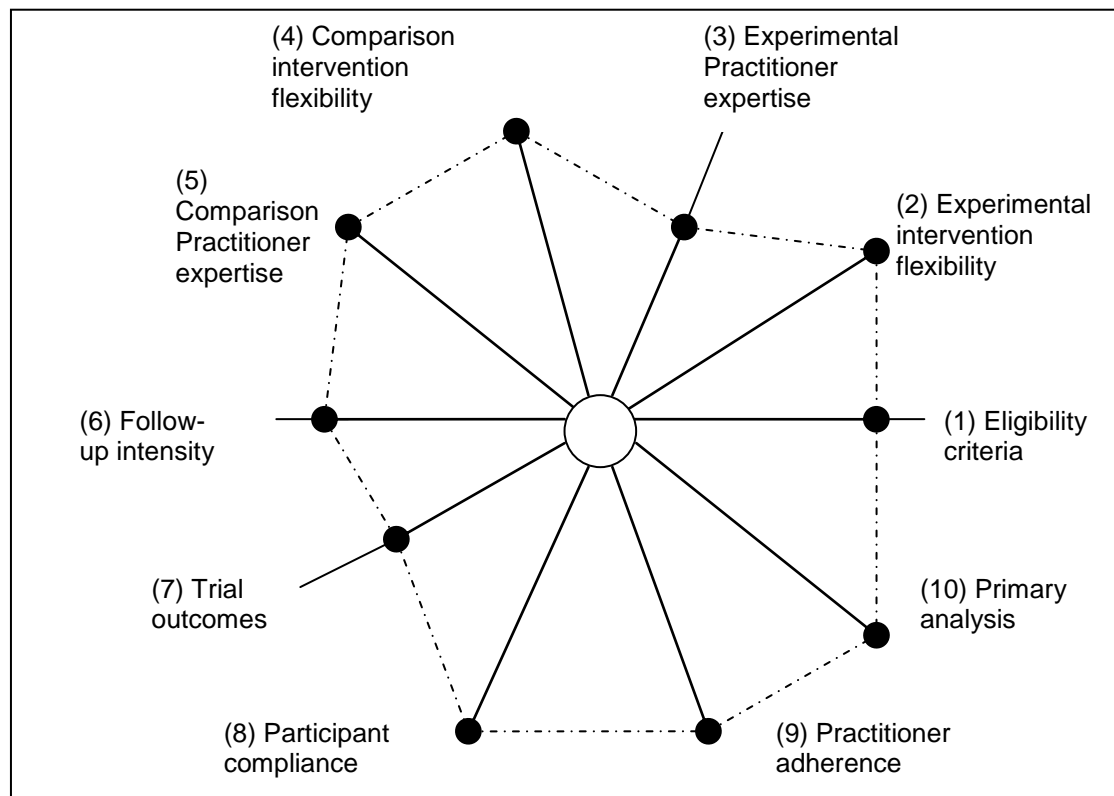
9.3.3   The PRECIS wheel and the 'Patient Cohort' RCT design

Diagram 9.2 depicts the PRECIS tool – the wheel – with the explanatory pole near the hub and the pragmatic pole on the rim. In this diagram the activities of the pilot of the Patient Cohort RCT design are depicted, showing whether the trial was narrowly focussed (near the hub) - asking whether the intervention can work under ideal circumstances, or tending to take a broader and more pragmatic view (near the rim) - asking whether an intervention does work under usual conditions. It can be seen in the diagram that the pilot took a broadly pragmatic view as it has been drawn on or near the rim for eight out of ten of the domains, the two exceptions being the practitioner expertise and trial outcomes domains. These two exceptions are due to the trial being a pilot rather than due to any limitations of the design. A full RCT using this design would be able to obtain long term outcomes and to recruit practitioners with

experience in this condition rather than experts. Thus a full RCT using the 'Patient Cohort' RCT design would be plotted on the pragmatic end of all ten domains, and thus would be evaluated as taking a fully pragmatic approach to the trial.

9.3.3   Limitations of the PRECIS tool

This evaluation represents the perspective of the PI, although to apply this tool correctly would perhaps require the design to be assessed by peers. Since the 'Patient Cohort' RCT design is a non standard RCT design (in that it has several recruitment stages), interpretation of the Participant eligibility criteria domain was difficult as each recruitment stages (the Cohort stage, the Eligible trial stage, the Offer stage) requires its own set of criteria. But overall, applying the tool to the pilot was relatively simple.

Consideration should perhaps be given to adding further domains to the ten existing domains in order to assess the following: the timing and type of information given, the consents sought in recruitment, how closely or not they replicate the procedures in routine healthcare (Key Criterion V Replicate the processes of routine healthcare, VI Patient appropriate information & VII Patient appropriate consent), and to assess the degree to which patient or practitioner decisions have been altered by the design (Key Criterion XI Patient and practitioner preferences remain unaltered).

9.4   Summary

The 'Patient Cohort' RCT design would be reported as being a trial of low or medium internal validity using the widely used JADAD tool and as an effectiveness trial using the Gartlehner efficacy vs effectiveness criteria for trial design. However, the objectives of this chapter were to identify the most appropriate tool for assessing the pragmatic purpose of the design and then

apply this tool to assess the pragmatic purpose of the design. The most appropriate tool (PRECIS) was applied to the pilot of the 'Patient Cohort' RCT design and an evaluation by the PI decided that the pilot of the design was at (or nearly at) the pragmatic pole of each domain for eight out of the ten domains.

Prior to the introduction of the PRECIS tool, RCTs were deemed to be pragmatic rather than explanatory in two aspects only. Firstly, did the research question posed by the trial aim to help decisions between healthcare options (as opposed to test causal research hypotheses), and secondly, was the intervention modelled in a pragmatic manner? If the answer to both these questions was yes, then the design was said to be pragmatic rather than explanatory. The PRECIS tool is a more sophisticated tool for assessing the pragmatic or explanatory purpose of a trial design, by evaluating not just two domains (the research question and the way in which the intervention is modelled) but ten domains in which triallists need to make trial design decisions.

The pilot of the 'Patient Cohort' RCT addresses a real world question that aims to help decision makers make decisions about healthcare options and has modelled the intervention in a generally consistent pragmatic manner, with the pilot of the design demonstrating the 'pragmaticness' of the decisions in at least eight out of the ten domains on the pragmatic-explanatory continuum as measured by the PRECIS tool.

Chapter 10   Discussion

10.1   Introduction

The aim of this thesis was to identify: *"What type of clinical trial design can provide the information needed to make decisions about the provision of homeopathy in a publicly funded healthcare system?"* A critique of the methods used in existing clinical trial designs was undertaken, which identified twelve key criteria for appropriate clinical trial design; methods from existing standard and alternative clinical trial designs were adapted in order to derive a new clinical trial design that attempts to meet all twelve key criteria (the 'Patient Cohort' RCT design); a current clinical question was identified through a review of the literature on treatments for menopausal hot flushes and confirmed with a population based survey; the 'Patient Cohort' RCT design was applied to this clinical question and the design was piloted and evaluated.

10.1.1   Aims and objectives

The aim of this chapter is to discuss the thesis expounded in chapters 1 to 9. The objectives of chapter 10 are to:

- Summarise the key findings of the thesis
- Assess the strengths and limitations of the thesis
- Discuss the generalisability of the key criteria, the findings of the pilot and the generalisability of the design

- Outline the challenges to the 'Patient Cohort' RCT design
- Draw conclusions and make recommendations for homeopathy research and clinical trial design

10.2 Summary of key findings

10.2.1 The NHS relevant components of homeopathy: treatment by a homeopath

The first finding of this thesis is the need to distinguish between several different possible meanings of the term 'homeopathy': the therapeutic system of homeopathy, the principles of homeopathy, treatment by a homeopath, and the homeopathic medicine and then to identify the components of relevance to the NHS. The question that has dominated 'homeopathy' clinical trials research has been the efficacy of homeopathic medicines, but publicly funded healthcare systems such as the NHS require information on the clinical and cost effectiveness of delivering homeopathy. Since homeopathy is delivered by 'homeopaths' (and homeopaths account for the bulk of the cost of NHS homeopathy) then the component of homeopathy that is of most relevance is not the homeopathic medicine but the whole package of care - 'treatment by a homeopath'.

10.2.2 The NHS clinical question: women with hot flushes

This thesis identified women with menopausal hot flushes who cannot or will not take HRT as a 'with need' patient group. Although there is observational evidence of the clinical effectiveness of treatment by a homeopath for women with menopausal hot flushes, this thesis identified that there is no RCT evidence of treatment by a homeopath.

10.2.3 Key criteria for appropriate trial design

Four perspectives were examined from which twelve criteria for appropriate trial design were derived, the majority of which relate to external validity issues.

From the perspective of the intervention, homeopathy in the NHS, two key criteria were identified: the need for pragmatic RCTs (I) that allow for the complexity and proper functioning of the intervention (II).

From the perspective of the condition, menopausal hot flushes, two further key criteria were derived: the need for the findings of RCTs to be generalisable to the 'with need' population (III) and the need for both long and short term outcomes (IV).

From the individual patient perspective on clinical trials, three key criteria were derived: the need for clinical trials to replicate the processes of routine healthcare (V) and have patient appropriate information (VI) and patient appropriate consent (VII).

From the current perspective of Health Services Research five further key criteria were identified: the need for clinical trials to have internal and external validity (VIII), to recruit sufficient numbers of patients (IX), to recruit patients who are representative of the reference

population (X), for patient and practitioner preferences to remain unaltered (XI) and for informed consent procedures to not be a barrier to recruitment (XII).

10.2.4 Existing clinical trial designs

Neither the standard pragmatic RCT design, nor ten existing hybrid or alternative designs meet all twelve criteria. However, the single randomised consent design meets eleven out of twelve

of the key criteria and the cohort aspect of the Comprehensive cohort study design facilitates the production of long term outcomes - key criterion (IV).

10.2.5 Appropriate trial design: The 'Patient cohort' RCT design

This thesis suggests that the 'Patient Cohort' RCT design is one that can meet all twelve key criteria. The 'Patient Cohort' RCT design combines two elements of existing trial designs:

- No information about treatment is given to patients prior to randomisation and post randomisation information is given only to those allocated to a treatment – a feature taken from the single randomised consent design.
- A large cohort of patients with follow up of all patients - a feature of the Comprehensive cohort study design

Further elements were added:

- Use of a large cohort of patients as a 'Within cohort multiple trials facility' which can then provide: information as to the normal progression of the disease and associated factors, long term outcomes, a facility for multiple trials, information on treatment as usual (TAU), increased comparability of research and strengthened statistical inferences.
- Patient Centred Information and Consent – which replicates the types and timings of the information given in routine healthcare, and the types and timings of the consents sought in routine healthcare. The advantage of this is that both information and consent are relevant to the patient's status as a patient, and thus appropriate relationships between patient and clinician are maintained.

Box 10.1 restates the brief definition of the 'Patient Cohort' RCT design.

Box 10.1   The 'Patient Cohort' RCT design

The 'Patient Cohort' RCT design consists of an observational Cohort of patients with the condition of interest within which multiple RCTs are embedded.

- **For each RCT, eligible patients are identified, a proportion of whom are then randomly selected to be offered the intervention.**
- **The outcomes of the selected eligible patients are compared to the outcomes of the non-randomly selected eligible patients**
- **Patient information and consent replicate the processes of routine healthcare wherever possible.**

10.2.6 Preliminary study of the 'Patient Cohort' RCT design

A pilot study was conducted of the 'Patient Cohort' RCT design applied to a current NHS question of clinical and cost effectiveness of treatment by a homeopath for women with menopausal hot flushes. A population survey of 1,214 women aged 45 – 64 was undertaken in order to identify the Hot Flush Cohort. Seventy women with frequent and severe menopausal

hot flushes women ('with need') were identified for the Hot Flush Cohort of whom 48 were eligible for the treatment and who thus became the 'Eligible' trial group. A proportion of this 'Eligible' trial group were randomly selected to be offered the treatment (who then became the Offer group). The rate of completion of 36-week outcome measures for the 'Eligible' trial group was high (93.7%), as was completion of the outcome measures and economic resource questions at 36 weeks (85.4% - 91.7%). The primary outcome measure appeared to be acceptable to patients with 95.8% of responders completing the HFFS at 36 weeks (which increased to 100% after two telephone calls to patients). 43/44 patients consented to have their data used at 36 weeks. 70.8% of the Offer group accepted the offer of treatment.

The pilot study was not sufficiently powered to detect (and did not detect) a clinically significant 10 point difference between the Offer and the No Offer group in the primary outcome measure using an intention to treat analysis. Analysis of the secondary outcome measures showed that patients in the Offer group reported some evidence of better EQ-5D scores (p= 0.05) compared to the No Offer group, and a positive trend for the Offer group was found for the GCS Total score & MYMOP Primary symptom score. CACE analysis produced a relative risk of 5.2 and 7.0 for a 5+ point and 10+ point reduction in the primary outcome measure for accepters of the offer of treatment. These results indicate that a full trial of this treatment in this particular condition is worth conducting.

10.2.7 Evaluation of the 'Patient Cohort' RCT design

Evaluation of the pilot of the design was limited due to the lack of any planned evaluation and the fact that the pilot was not a full test of the 'Patient Cohort' RCT design. A *post hoc* evaluation of the pilot of the design was conducted with regards to whether 'it worked', that is to say, was it in essence an ultra-pragmatic RCT design? The evaluation plotted the pilot of the design on the ten domains of the pragmatic-explanatory continuum of the PRECIS tool (Thorpe et al. In press) and found that the design was at (or nearly at) the pragmatic pole of eight out of the ten domains of the pragmatic-explanatory continuum.

10.3   Strengths and limitations of the thesis

10.3.1   Strengths of the thesis

Timeliness

This thesis has addressed several timely methodological issues. Firstly, the Chair of NICE, Professor Sir Michael Rawlins, in his Harveian oration to the Royal College of Physicians (2008) http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=262 (accessed 11.12.08) makes a plea to investigators to *"continue to develop and improve their methodologies"* in order to help

decision makers appraise the evidence and make judgements as to which components of the evidence base are 'fit for purpose', reliable, and generalisable. Secondly, the House of Lords' 6th Report on Complementary and Alternative Medicine (2000) recommended that *"new research strategies which are sensitive to the CAM paradigm need to be developed".* This thesis has developed and tested a new research strategy - the 'Patient Cohort' RCT design – a set of methods which may help healthcare decision makers more easily make the judgements they need to make in appraising the evidence from clinical trials but which is also sensitive to one particular CAM modality, 'homeopathy'.

Many specific questions of current interest have also been addressed such as: how to assess the clinical and cost effectiveness of homeopathy in the NHS? What are the alternatives to HRT for women with frequent/severe menopausal hot flushes? How can patient recruitment to trials be improved? How to make the results of trials more generalisable to routine healthcare situations?

An empirical test of an innovative clinical trial design

This thesis has employed a wide range of methods, incorporating secondary as well as primary research with an initial methodological enquiry and an empirical test of an innovative clinical trial design in its approach to a complex research question.

10.3.2   Limitations

Perspectives on standard clinical trial designs

The four chosen perspectives were examined by using secondary research. However, this examination could be strengthened by using primary research methods to investigate stakeholders' views, e.g. questionnaires, interviews, Delphi techniques. Other perspectives could also be identified and examined e.g. the research commissioners, clinicians making decisions about individual patients, or those who implement IC procedures, until saturation is reached.

Not a full test of the design

This thesis reports only a partial test of the 'Patient cohort' RCT design. A full test would study the application of the design, identify a situation where the greatest advantages of the design could be tested (a chronic long term condition where significant numbers of trials were sought/planned) and thus enable stronger conclusions regarding the 'Patient Cohort' RCT design to be drawn.

Lack of planned evaluation

During the writing of the protocol, the key criteria for appropriate trial design were implicit rather than explicit, and thus there was no direct or robust assessment of how well the design met the

twelve key criteria, or of how well the key features of the 'Patient Cohort' design actually worked in practice. Evaluation of these key features would benefit from a prospective evaluation using qualitative or observational ethnographic study in parallel to a full study in order to provide insights into a variety of questions and help to contextualise the results. Such questions might be, why or how the treatment was or was not effective, what was the impact of being offered treatment by someone not involved in the patient's routine healthcare, and what were patients views on the trial design, particularly with regard to the withholding of information about the treatment group?

10.4   Generalisability

This section discusses the generalisability of the key criteria, the findings of the pilot, and the generalisability of the design.

10.4.1. Generalising of the key criteria

This thesis does not claim that the twelve key criteria represent all key criteria from all perspectives. For example, one unexamined perspective is that of the clinician making a decision about a particular patient's treatment who would therefore wish for clinical trials to provide information to help decide whether a particular treatment is the best treatment for a particular patient in a particular set of circumstances. Primary research methods (e.g. Delphi method) might also derive further key criteria from examined and as yet unexamined perspectives. Although the twelve key criteria are not universally held, many of the criteria identified do overlap with each other (e.g. recruit patients who are representative of the 'with need' population (X) overlapping with, the need for the findings of RCTs to be generalisable to the 'with need' population (III)). Thus exploring further perspectives might not reveal many more key criteria.

10.4.2   Generalisability of the findings of the pilot

The findings from the empirical study will inform the design of the main study. GP database recruitment is an effective method of identifying this particular 'with need' group, as women aged 45 – 64 years are a stable and easily identifiable patient group who are also known to be good responders to postal questionnaires. The acceptance rate for this intervention was high, but women in this age group are high users of CAM. The response rates and acceptance rates found in the pilot, though generalisable to women of this age group, are not necessarily generalisable to other patient groups, conditions or treatments.

10.4.3   Generalisability of the 'Patient Cohort' RCT design

The 'Patient Cohort' RCT design appears to be a workable and useful design with regards to the pragmatic purpose of the research (i.e. to "..provide the information needed to make decisions about the provision of homeopathy in a publicly funded healthcare system"), and the

particular intervention and condition in which a limited version of the design was piloted. How workable and useful is the design with regards to other circumstances, questions, interventions and conditions? The following sections explore the circumstances, questions, interventions and conditions where the 'Patient Cohort' RCT design is most and least suited.

10.4.4 Circumstances

The 'Patient Cohort' RCT design is best suited to circumstances which require open rather than closed trial designs where TAU is compared to the offer of treatment, e.g. Traditional acupuncture versus usual care (Thomas et al., 2006). It is less suited to head-to-head trials e.g. a homeopathic complex remedy versus xylometazoline (Ammerschlager et al., 2006).

10.4.5 Questions

As the 'Patient Cohort' RCT design is an ultra-pragmatic trial design, it is obviously most suited to pragmatic questions. As Thorpe et al. (In press) point out, many of the decisions with regards to individual trial components can be placed on a pragmatic - explanatory spectrum. As an ultra-pragmatic RCT design, this design is least suited to addressing efficacy questions, i.e. trials which use placebos and which are thus at the explanatory end of the pragmatic - explanatory spectrum. However, the design could be adapted to incorporate an efficacy trial (in the within cohort multiple trials facility) if estimates of both effectiveness and efficacy were needed, but since the current norm dictates that patients must be given prior information that they may be randomised to receive placebo then such a trial would thus lose the benefits of the Patient Centred Informed Consent procedures of the design.

Since outcomes are collected from large numbers of patients, the design is most suited to questions where outcomes can be easily collected and easily measured, e.g. wellbeing scores, quality of life scores, weight, waist measurement, economic outcome measures etc.; the majority of which are Patient Reported Outcome Measures (PROMS). The design is least suited to questions which require 'hard to measure' outcomes or invasive tests such as diagnostic tests which require patients to be tested in clinic, e.g. the Tender Point Count for a diagnosis of Fibromyalgia Syndrome (FMS); many 'hard to measure' outcomes are non patient reported outcome measures (non-PROMS).

10.4.6 Clinical conditions

One unique feature of this design is the multiple trials facility, a feature which makes the design suited to conditions or patient groups where many pragmatic trials are being planned[53]. The longer the time period over which the cohort of patients is studied, and the more trials that use the cohort, the more efficient will be the cohort in reducing trial treatment costs, fewer patients

---

[53] Use of such a multiple trials facility will require both the number and size,of possible trials to be estimated. Separate funding for the cohort and for individual trials may be needed, perhaps with each trial paying into the cohort in order to be able to use its multiple trials facility. It would be sensible to associate funding and priority setting with the funding streams that support the provision of healthcare services in terms of questions and possible trial treatments.

will be offered experimental interventions with uncertain outcomes, and there will be increased comparability of the results between trials.

The design facilitates the collection of long term outcomes, and thus this design will be useful where long term outcomes are required such as in chronic conditions and prevention research. For example, the MRC under the National Prevention Research Initiative: Phase 3 http://www.mrc.ac.uk/ApplyingforaGrant/CallsForProposals/NPRI3/index.htm accessed 18.8.08, has made £12mn available to fund research aimed at improving health and at preventing obesity, heart and circulatory diseases, diabetes, stroke and dementia.

The design is generally more suited to chronic rather than acute conditions, partly because chronic conditions require longer term outcomes and partly because chronic conditions (by definition) rarely resolve, with the result that there will be less need for replenishment of the cohort. Conversely, short term conditions usually require short term outcomes, and a cohort of patients with a short term condition will require continual replenishment of the cohort due to the frequent resolution of the condition.

The design is more suited to stable, easily identified populations as outcomes are more easily obtained from such populations. The design is also more suited to conditions with poor recruitment, e.g. pregnant women (Rodger et al., 2003), as the patient centred informed consent procedures will be more acceptable to patients.

10.4.7 Treatments

The design is most suited to testing desirable treatments in which the offer of treatment is likely to be accepted, and the more desirable the treatment the greater the potential for this type of randomised consent design to be used. Conversely, the design is least suited to undesirable treatments as the larger the non compliance with the offer of the intervention, the greater the chance of a Type II error (underestimating the true effects of a treatment).

The design is also suited to testing expensive treatments, and likewise, the more expensive the treatment the greater the rationale for the design. The potential of the design for unequal randomisation potential means that fewer (expensive) treatments need to be provided in order to adequately power a trial than with standard designs, thus reducing the trial treatment costs overall. A simple method of calculating the allocation ratio for unequal randomisation based on cost is the square root of the cost ratio of the treatments being compared (Torgerson & Torgerson, 2008).

For trials of expensive treatments e.g. £5,993 for gastric banding for extreme obesity http://www.dh.gov.uk/en/FreedomOfInformation/Freedomofinformationpublicationschemefeedback/FOIreleases/DH_4112482 accessed 1.12.08) the large numbers of patients recruited to an observational cohort (and thus the ability to use unequal randomisation) means that fewer patients need to be in the treatment group than with designs using equal (1:1) randomisation. Thus the design will make significant cost savings for expensive treatments compared to RCT designs with equal randomisation.

Box 10.2   Where the design is most and least suited

Most suited to:	**Least** suited to:
Circumstances	**Circumstances**
• Open trials with TAU as comparator	• Closed trial designs with masking and/or placebo
Questions	**Questions**
• Pragmatic questions	• Efficacy type questions
• With easily measured & collected outcomes	• With hard to measure & hard to collect outcomes
Clinical conditions	**Clinical conditions**
• Where many clinical trials will be conducted	• Acute or short term conditions
• Chronic conditions	• High attrition/unstable patient populations
• Stable populations	• Difficult to identify populations
• Easily identified populations	
• Conditions with poor recruitment	
Treatments	**Treatments**
• Desirable treatments	• Undesirable treatments
• Expensive treatments	

However, the merits of the design mean that it may be advantageous in situations where none of these situations apply; the pilot of the 'Patient Cohort' RCT was conducted in a short term condition – menopausal hot flushes – but compared to a standard RCT was able to recruit quickly and cheaply, and probably acquired a trial more representative of the 'with need' population. Box 10.2 lists the conditions that the 'Patient Cohort' design is most and least suited to.

10.5   Challenges to the 'Patient Cohort' RCT design

10.5.1 The norm for RCTs

The terms, methods, procedures and evaluation tools for clinical trials were developed in an era when explanatory/efficacy trials were the norm but the terms, methods etc., of that era are not always easily applied to pragmatic/effectiveness trials. The aim of the 'Patient Cohort' RCT design is to replicate as far as possible, real world clinical practice in all the pre trial and trial processes in order to create a design that can assess the benefit of treatments to patients. In attempting to do this, the 'Patient Cohort' RCT challenges many of the conventional ways of describing and evaluating RCTs and revisits and redefines some concepts and terms. Take for

example, the concept of 'being in a trial', what does that really mean for a patient? Does the term 'Informed Consent' imply full or just relevant information (and relevant to whom)? Pragmatic trials ask questions with the aim of providing answers about the real world, and interventions in pragmatic trials are usually modelled on real world clinical practice, but this thesis argues that pragmatic trials need the processes in and around clinical trials to be modelled (wherever possible) on real world practice as well.

10.5.2   Non compliers and ITT analysis

A key difference between the standard and 'Patient Cohort' RCT design is that standard RCT design screens out potential non compliers by providing full information to all trial patients as to the treatments they might receive <u>prior</u> to randomisation; the advantage of this is that the number of non compliers recruited to the trial is minimised. However, the 'Patient Cohort' RCT does not do this (as this does not happen in routine healthcare), and thus the design is less able to screen out potential non compliers as in the pilot, where 70.8% of the Offer group accepted the offer of treatment. In order to maintain the advantages of randomisation, an ITT analysis must be conducted as this is the most robust analytical method. However, for any trial, if compliance with the treatment is less than 100% (as it was in the pilot) then an ITT analysis may underestimate the true treatment effect and thus run the risk of a Type II error (concluding that there is no difference between the groups when in reality there is a difference). Thus the main weakness of the 'Patient Cohort' RCT design is that if there are patients who decide not to accept the offer of treatment, then an ITT analysis runs a high risk of a Type II error.

There are various ways that this risk could be reduced. For example, patients could be recruited from treatment seeking populations, or patients could be asked whether they are looking for treatment, or what types of treatment they are looking for. However, care would need to be taken to avoid asking leading questions, which might result in patient's expecting to be offered a particular treatment (when they might then not be offered).

Pragmatic trials need to produce a variety of answers to the question 'is treatment X clinically and cost effective?': is it deliverable (by practitioners in an NHS setting)?, is it acceptable to patients?, do patients comply with the treatment?, what is the effect of the treatment?, what is the cost of the treatment? how safe is the treatment? Thus to reduce the results of a pragmatic trial to one single ITT analysis with a single dichotomous yes/no answer as to the effect of the treatment on the whole trial population will lose a lot of useful information. Patients, clinicians, and commissioners will also want to know the effect of the treatment on those who accept the treatment. ITT analyses such as per protocol analysis etc., lose the advantages obtained by the initial randomisation and thus reduce the internal validity of the research. The conflict between internal validity and accuracy of the estimate of effect is perhaps to some degree resolved by a different type of analysis, Complier Average Causal Effect analysis (CACE) (Hewitt et al., 2006) which retains the benefits of randomisation, but makes two assumptions. Thus CACE analysis

measures the average causal effect for the subpopulation of compliers and preserves the benefits of the initial randomisation. However, it does make two assumptions: firstly, that the compliance rate in the control group would be the same as the compliance rate in the treatment group *if* they were offered the treatment and secondly, that the offer of treatment itself does not affect outcomes (see section 8.2.14 & 8.3.14 & 8.3.15).

10.5.3 Who offers the treatment being trialled?

One challenge to the '"pragmaticness"' of the 'Patient Cohort' RCT design is the issue of who offers the treatment being trialled? In routine healthcare, the patient's clinician would offer the treatment to the patient; however, in a fully pragmatic RCT this would require clinicians to offer treatments to patients at random (requiring both clinician and patient to be in constant equipoise and well organised – an unlikely scenario). If this was not possible then clinicians could be randomly chosen to either offer a treatment or not as is the case with individual-cluster RCTs.

10.5.4 Institutional acceptability of the 'Patient Cohort' RCT design

Various types of UK institutional approval are required to conduct NHS trials: NHS Scientific review, MHRA and NHS Ethics committee. How acceptable is the 'Patient Cohort' RCT design to these authorities? The experiences of the pilot of the design are described below.

NHS Scientific Review: NHS Scientific review approval was sought from the NHS Sheffield Health and Social Research Consortium Scientific Review Committee. During five months of discussions, the Review committee wanted the research to address *'whether homeopathic treatments are effective per se'* (an efficacy of homeopathic medicines question) and argued strongly for an explanatory type double blind placebo RCT design since *'the methodology is widely used, accepted and understood'.* NHS Scientific Review Approval was finally obtained on 5.9.06 (Consortium ref: ZF89). It was unclear whether the source of the difficulties was the controversial nature of the intervention being trialled or reluctance to use a pragmatic (rather than explanatory) trial design.

Medicines Health Regulatory Authority (MHRA): NHS ethical approval required a decision from the MHRA as to whether the trial needed MHRA approval. Consulting the algorithm for clinical trials published by the MHRA *'Is it a clinical trial of a medicinal product?'* did not aid the decision
([http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con009394.pdf accessed 30.4.08](http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con009394.pdf)).
The MHRA first advised that the trial was registered as a Clinical Trial of an Investigational Medicinal Product (CTIMP) and that just one homeopathic medicine was named as the IMP despite the fact that a number (30+) of homeopathic medicines from a pharmacopoeia with 2,000+ homeopathic medicines would be used in the trial. The idea of giving inaccurate information to the MHRA despite their advice (combined with the prospect of the MHRA £250

fee) led the PI to continue searching for a more coherent decision from the MHRA. Two months of discussions with the MHRA led to the decision that the trial was *not* a CTIMP and therefore did not require Clinical Trials Authorisation. The MHRA rationale for this decision was that the protocol stated that the primary statistical analysis was an Intention to Treat (ITT) analysis of those *offered* the treatment compared to those *not offered* the treatment, clarifying therefore it was not a trial of a treatment (an IMP) but of the offer of treatment. One wonders whether the same decision would have been reached if the trial had been a trial of the offer of Seroxat or chemotherapy? Although technically correct the decision still seems to lack coherence. The core problem seems to be that MHRA procedures are designed for standard trials where the offer of treatment is <u>prior to the official start of the trial</u> so the 'Patient Cohort' RCT just did not fit their procedures, and is thus an example of the design challenging the norm.

NHS Ethics review: The protocol was initially rejected by North Sheffield NHS Research Ethics Committee who made similar recommendations to those of the NHS Scientific Review. The study protocol was revised to increase the clarity of its presentation, but neither the aims nor design was changed. The revised study protocol was resubmitted to South Sheffield NHS Research Ethics Committee and approved.

These experiences confirm other researchers experiences that currently scientific review committees and ethics committees are more familiar with traditional explanatory (placebo) trials and have relatively limited experience of pragmatic trials (Tunis et al., 2003). The MHRA experience is an example of the design challenging the norm with regards to definitions of terms and procedures.

10.5.5 Ethical challenges

The Informed Consent procedures used in standard RCT designs are seen as ethically acceptable by ethics committees, but these committees may be reluctant to authorise an unusual RCT design such as the 'Patient Cohort' RCT design. In order for such a design to be considered, there needs to be greater consideration of the ethics of the Informed Consent procedures of standard RCT designs. This section highlights these issues, discusses how the 'Patient Cohort' RCT design addresses them, and offers a way forward for improving the ethics of the 'Patient Cohort' RCT design.

Existing issues

Several types of alternative trial designs have been developed in order to avoid ethical issues in clinical trials: Clinician preferred treatment, Patient preference trials, and Randomised Consent Designs (such as the 'Adapted randomised consent (Zelen) design' and the 'Patient Cohort' RCT design). Clinician preferred treatment trials and Patient preference trials, although more ethical from the patient/clinician perspective, do not increase the proportion of people recruited to the randomised arms and are thus not an overall improvement on standard RCT design.

Addressing the issues

Randomised Consent Designs such as the 'Patient Cohort' RCT design which attempt to improve standard RCT design, have two ethical advantages in that patients do not have to consent to a state of uncertainty as to treatment allocation, and are not informed about a treatment that they then may not receive.

The use of Randomised Consent Designs in the clinical areas of cancer, neonatology and heroin dependency, has been justified by arguing that not seeking informed consent prior to randomisation reduces both anxiety and distress for the patient and contamination between groups for highly desired treatments. This thesis suggests that if this argument is valid for cancer and neonatology then surely it is equally valid for other diseases and patient groups. Likewise if the above argument holds true for highly desired treatments then it also holds true (though to a lesser degree) for moderately or slightly desired treatments.

The ongoing recruitment difficulties for standard design clinical trials an indication of the lack of resolution of two issues with standard Informed Consent procedures: how ethical is it to ask patients to consent to a state of uncertainty with regards to which treatment they are going to receive? and how ethical is it to tell patients about a 'possible' treatment only to then tell them that they are not going to receive it? –a recently debated question in the BMJ (Marcus, 2007; Firth, 2007).

10.5.6   A possible solution to the ethical issues

One possible solution to these ethical issues is to borrow from the methods used in cluster RCT designs, designs with strong similarities to the 'Patient Cohort' RCT design in that both have a large group of patients (cluster/Cohort) and neither seek consent (to treatment) from individuals prior to randomisation/random selection. Lack of consent to randomisation from individuals is not seen as an insurmountable ethical issue for cluster RCTs (Torgerson & Torgerson, 2008), yet lack of prior consent to randomisation from individuals is regarded as controversial for Randomised Consent Designs. For cluster RCTs, Edwards et al. (1999) argue that the role of guardian is key to their ethical conduct, so perhaps Randomised Consent Designs such as the 'Patient Cohort' RCT design should likewise appoint a guardian to look after the interests of the population being researched (the Cohort). For example, a GP or GPs could be appointed in order to ensure the safety and rights of those patients, or alternatively, guardian(s) could be drawn from the Cohort of patients in order to approve trials on behalf of the Cohort.

In the pilot, GPs invited their patients to participate in the observational research, but were not consulted during the planning stage of the pilot RCT stage. It could be argued that the appointment of a guardian for the 'Patient Cohort' would have safeguarded the interests of these patients at all stages in the pilot of the 'Patient Cohort' RCT design.

10.5.7   Future use of the 'Patient Cohort' RCT design

The NIHR have provided £10mn to seven Collaborations for Leadership in Applied Health Research and Care (CLAHRCs) **http://www.nihr.ac.uk/infrastructure_clahrcs.aspx** accessed 18.8.08. These collaborations have been established to undertake high-quality

applied health research focused on the needs of patients and to support the translation of research evidence into practice in the NHS. The South Yorkshire Applied Research & Care Consortium (SYARCC) CLAHRC is focussing on five long term conditions including obesity. Since January 2009, Clare Relton has been employed at the University of Sheffield, by the Principal Investigator of the CLAHRC obesity theme (Dr Paul Bissell), to develop a study of obesity using the 'Patient Cohort' RCT design, using the methods developed and reported in this thesis.

10.6 Conclusions and recommendations

10.6.1 Conclusions and recommendations for homeopathy research

Clarity in use of the term 'Homeopathy': The term homeopathy has multiple meanings. However, the current level of abstraction[54] of all the elements of the therapeutic system of homeopathy to just a single term 'homeopathy' has muddied thinking regarding homeopathy research. Systematic reviews of 'homeopathy' lack clarity as they confound different meanings of the term - homeopathic medicine, treatment by a homeopath, the principles of homeopathy, and the therapeutic system of homeopathy. Clarity as to which meaning is being used is needed when discussing 'homeopathy' research.

Recommendations for homeopathy research:
- In reporting research, the exact aspect of 'homeopathy' being discussed is made explicit and the term 'homeopathy' should be solely used to refer to the 'therapeutic system of homeopathy'.
- In debates regarding 'homeopathy', the evidence referred to should match the evidence required by the nature of the question being debated.

Introduction of further MeSH terms for the homeopathy field: The introduction of additional MeSH terms: homeopath, homeopathic medicine, the principles of homeopathy, the therapeutic system of homeopathy – and their precise use in the reporting of homeopathy research – would greatly improve the quality of understanding in this area. This would improve the design and conduct of 'homeopathy' trials and lend clarity as to what can be inferred when reviewing and interpreting 'homeopathy' trials.

Recommendations for homeopathy research:
- Four new additional MeSH subheadings should be introduced: homeopathic medicine, treatment by a homeopath, the principles of homeopathy and the therapeutic system of homeopathy.

---

[54] The process of generalising the information content of a concept in order to retain only information which is relevant for a particular purpose

Building the evidence base: The clinical 'homeopathy' evidence base currently relates to the efficacy of homeopathic medicines rather than the effectiveness of treatment by a homeopath, and efficacy established in ideal conditions is not necessarily the same as effectiveness in real world routine conditions. If RCTs and systematic reviews are to be used to inform clinical decision making and NHS resource allocation decisions, then evidence of the clinical and cost effectiveness of being treated by a homeopath is needed. However, there is no published trial evidence of the effectiveness of being treated by a homeopath[55]. Given that the provision of NHS 'homeopathy' is contested, there is a priority for building an evidence base for 'homeopathy' in NHS settings i.e. treatment by a homeopath, and this will need trials of treatment by a homeopath with designs that allow the complexity and proper functioning of the intervention.

Recommendations for homeopathy research:

- Pragmatic RCTs of treatment by a homeopath need to be conducted in order to inform decision making regarding the provision and use of 'homeopathy'.
- The pilot results indicate that there may be benefit in conducting a full RCT to assess the clinical and cost effectiveness of treatment by a homeopath for women with frequent/severe menopausal hot flushes who cannot take HRT.

10.6.2 Conclusions and recommendations for clinical RCTs

An ultra-pragmatic RCT design

The 'Patient Cohort' RCT design is an ultra-pragmatic RCT design for addressing questions as to the clinical and cost effectiveness of treatments in publicly funded healthcare systems such as the NHS. The design is especially useful for complex interventions and interventions where the therapeutic relationship may be one of the active ingredients. The 'Patient Cohort' RCT design (and other Randomised Consent Designs) have two ethical advantages in that patients are not informed about a treatment that they then may not receive and do not have to consent to uncertainty as to treatment allocation.

Recommendations for clinical RCTs

- The unresolved ethical issues of standard RCT designs (informing patients about treatments they may not receive and asking patients to consent to uncertainty as to treatment allocation) need to be thoroughly debated by all stakeholders in clinical trial design – patients, clinicians, academics, research commissioners, funders, users, and ethics committees. Additionally, the ethics of Randomised Consent Designs need to be revisited in this debate.

---

[55] apart from Owen, 1990.

- Further primary research is required to verify the findings of the literature review reported in chapter 4 regarding the reasons why patients participate in clinical trials.
- Informed Consent procedures should regard people in clinical trials primarily as patients rather than participants. Consideration should be given to the idea of substituting the term 'patient' for the term 'participant' in all clinical trial documentation (Protocols, Informed Consent Guidance, Trial reports etc.).
- Consideration should be given to using Patient Centred Information and Consent procedures instead of the current standard Informed Consent procedures.

Pragmatic trials require pragmatic procedures

Pragmatic trials are primarily designed to determine the effects of an intervention under usual conditions, and interventions in pragmatic trials are modelled to reflect usual conditions as much as possible, yet current procedures (authorised by NHS Scientific Review, NHS Ethics committees and NRES Guidance) produce trials that are not conducted under usual conditions for either patients or clinicians. For a trial to be truly pragmatic the processes of routine healthcare should be replicated wherever possible. The 'Patient Cohort' RCT design seeks to minimise the disruption to routine healthcare by the trial processes, while retaining the scientific advantages of randomisation.

Recommendations for pragmatic clinical RCTs

- The recruitment of a cohort of patients with the condition of interest should be considered, particularly in pragmatic questions with easily measured and collected outcomes, in clinical conditions where many trials will be conducted.
- Further research is needed to understand the issues for patients with regards to their data being used comparatively e.g. whether explicit permission to use data comparatively is required, in order to assess the rate at which patients will (or not) comply with such a request.
- It is recommended that a full test of the design is conducted, with a planned evaluation, in a question that requires an ultra-pragmatic RCT approach. Qualitative or observational ethnographic study undertaken in parallel will be needed in order to understand various aspects of the design, e.g. the impact of the different types of information given and consents sought, the impact of being offered treatment by a non routine healthcare provider, patient's views on withholding of information about the treatment group etc.
- The advantages and disadvantages of the 'Patient Cohort' RCT design compared to the standard pragmatic RCT design should be evaluated in a 'trial of trials'.
- Future use of Randomised Consent Designs (such as the 'Patient Cohort' RCT design) should consider the appointment of a guardian or guardians to look after the interests of the population (the Cohort) being researched

References

ABC of Complementary Medicine (2008), Zollman, C., Vickers, A., Richardson, J. (eds.), BMJ Books (Second edition).

AcademyHealth (2000), 'Health Services Research Projects in Progress', www.academyhealth.org/hsrproj/definitionofhsr.htm.

Adamson, J., Cockayne, S., Puffer, S. et al. (2006), 'Review of randomised trials using the post-randomised consent (Zelen's) design', Contemporary Clinical Trials, 4, 305-319.

Allmark. P. (1999), 'Should Zelen pre-randomised consent designs be used in some neonatal trials?', Journal of Medical Ethics, 25, 325-329.

Altman, D.G., Whitehead, J., Parmar, M.K.B. et al. (1995) 'Randomised consent designs in cancer clinical trials', Eur J Cancer, 31A,1934-44.

Altunc, U., Pittler, M.H., Ernst, E. (2007), 'Homeopathy for childhood and adolescence ailments: systematic review of randomized clinical trials', Mayo Clinic Proceedings, 82, 1, 69-7.

Ammerschlager, H., Klein, P., Weiser, M., et al. (2005), 'Treatment of inflammatory disease of the upper respiratory tract – a comparison of a homeopathic complex remedy with xylometazoline', Forschende Komplementarmedizin und Klassiche Naturheilkunde, 12, 1, 24-31.

Anon. (1984), 'Consent: how informed?', Lancet, 1, 1445-7.

Appelbaum, P.S., Roth L.H., Lidz, C. (1982), 'The therapeutic misconception. Informed consent in psychiatric research', International journal of law and psychiatry, 5, 319-29.

Ashcroft, R.E, Chadwick, W.D., Clark, S.R.L. et al. (1997) 'Implications of socio-cultural for the ethics of clinical trials', Health Technology Assessment, Volume 1, No 9.

Ballard, K. (2002), 'Women's use of hormone replacement therapy for disease prevention; results of a community survey'. BJGP, 52, 835-837.

Barnes, J., Resch, K. L., Ernst, E. (1997), 'Homeopathy for postoperative ileus: a meta-analysis', Journal of Clinical Gastroenterology, 25, 4, 628-633.

Bartlett, C., Doyal, L., Ebrahim, S. et al. (2005), 'The causes and effects of socio-demographic exclusion from clinical trials', Health Technology Assessment, 9, 38.

Baum, M., et al. (2006), http://www.senseaboutscience.org.uk/pdf/Baum%20letter.pdf

Bell, I.R., Lewis, D.A., Brooks, et al. (2004), 'Improved clinical status in Fibromyalgia patients treated with individualised homeopathic remedies versus placebo', Rheumatology, 43, 5, 577-582.

Belon, P., Cumps, J., Ennis, M. et al. (1999), 'Inhibition of human basophil degranulation by successive histamine dilutions: results of a European multi-centre trial', Inflammation Research. 48, 1, 17-8.

Belon, P., Cumps, J., Ennis, M. et al. (2004), 'Histamine dilutions modulate basophil activation.' Inflammation Research, 53, 5, 181-8.

Black, N. (1997), 'Health services research: saviour or chimera?', Lancet, 349,1834-36.

Blatt, M.H., Wiesbader, H., Kupperman, H.S. (1953), 'Vitamin E and climacteric syndrome', Archives of Internal Medicine, 7, 92-9.

BMS (2002), 'Management of the Menopause: The handbook of the British Menopause Society' (eds Rees, M., Purdie, D.), BMS Publications Ltd,

Boon, H., MacPherson, H., Fleishman, S. et al. (2006), 'Evaluating complex healthcare systems: a critique of four approaches', eCAM doi:10.1093/ecam/ne1079.

Born, G., Baum, M., Colquhoun, D. et al. (2007) www.timesonline.co.uk/tol/life_and_style/health/article1827553.ece

Börnhoft, G., Wolf, U., Ammon K., et al. (2006), 'Effectiveness, safety and cost-effectiveness of homeopathy in general practice - summarized health technology assessment'. Forschende Komplementärmedizin, 13 S2,19-29.

Boter, H., van Delden, J.J.M., de Haan, R.J. (2004), 'Patients' evaluation of informed consent to postponed information: a cohort study' BMJ, 329, 86.

Bowers, D. (2002), Medical statistics from scratch. WileyBlackwell.

Brazier, J.E., Roberts, J., Platts, M. et al. (2005), 'Estimating a preference-based index for a menopause specific health quality of life questionnaire'. Health and quality of life outcomes 3:13 doi:10.1186/1477-7525-3-13

Brekke, O.A., Sirnes, T. (2006), 'Population biobanks: The ethical gravity of informed consent', Biosocieties, 1, 385-398, London School of Economics and Political Science doi:10.1017/S1745855206004029

Brewin, C.R., Bradley, C. (1989), 'Patient preferences and randomised clinical trials', BMJ, 299, 313-315.

British National Formulary March 2000, The Pharmaceutical Press, London.

Britton, A., McKee, M., Black, N. et al. (1998), 'Choosing between randomised and non randomised studies: a systematic review', Health Technology Assessment, 2, 13.

Campbell, R., Peters, T., Grant, C. et al. (2005), 'Adapting the randomised consent (Zelen) design for trials of behavioural interventions for chronic disease: a feasibility study', Journal of Health Services Research Policy, 10, 4.

Campbell, M. (2007), 'Recruitment to randomised trials: Strategies for trial enrolment & participation study (STEPS)' http://www.hta.nhsweb.nhs.uk/project/1564.asp (accessed 6.11.07)

Campbell, N.C., Murray, E., Darbyshire, J. et al. (2007), 'Designing and evaluating complex interventions to improve healthcare', BMJ, 334, 455-459.

Carpenter, J.S., Andrykowski, M.A., Freedman, R.R. et al. (1999), 'Feasibility and psychometrics of an ambulatory hot flash monitoring device', Menopause, 6, 209–215.

Carstairs, V. (1995) 'Deprivation indices: their interpretation and use in relation to health' J Epidemiol Community Health, 49,S2,S3-8.

CASS (1984), Principal Investigators and their Associates. 'Coronary Artery Surgery Study (CASS): a randomised trial of coronary artery bypass surgery. Comparability of entry characteristics and survival in randomized patients and nonrandomized patients meeting randomization criteria', Journal of American College of Cardiologists, 3, 114- 128.

Chalmers, I. (1995), 'What do I want from health research and researchers when I am a patient?', BMJ, 310,1315-1318.

Chatwin, J.R. Collins, S. (2002), 'Studying Interaction in the Homeopathic Consultation'. The Homeopath, 24-26.

Clover, A., Ratsey, D. (2002), 'Homeopathic treatment of hot flushes: a pilot study', Homeopathy 91, 75-79.

Coleman, P. (2003) 'Access to Complementary and Alternative Medicines (CAMs) via primary care in England in 2001, and changes since 1995' Report to the Department of Health. MCRU, University of Sheffield.

Coulter, M.K., Dean, M.E., Gilbody, S. (2006), 'A systematic review of homoeopathy for attention-deficit hyperactivity disorder/ hyper-kinetic disorder', Focus on Alternative and Complementary Therapies, 11, 1, 15.

Creswell, J.W. (2003), 'Research Design: Qualitative, Quantitative and Mixed Methods Approaches', Sage Publications, USA (Second edition).

Criscione, L.G., Sugarman, J.S.L., Pisetsky, D.S.St.C. et al. (2003), 'Informed consent in a clinical trial of a novel treatment for rheumatoid arthritis', Arthritis & Rheumatism, 49, 3, 361-7.

Crombie, I.K., Davies, H.T.O. (1996), 'Research in healthcare: Design, conduct and interpretation of Health Services Research', Chichester, John Wiley & Sons.

Crow, H., Gage, H., Hampson, S. (1999), 'Measurement of Satisfaction with Health Care: implications for practice from a systematic review of the literature', Health Technology Assessment, 6, 32.

Crow, R., Gage, H,, Hampson, S. et al. (2002), 'The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature'. Health Technology Assessment, 6, 32.

Cucherat, M., Haugh, M.C., Gooch, M. et al. (2000), 'Evidence of clinical efficacy of homeopathy. A meta-analysis of clinical trials'. Homeopathic Medicines Research Advisory Group. European Journal of Clinical Pharmacology, 56, 1, 27-33.

Dawkins, R. 'Enemies of Reason' Channel 4, Shown on 20.8.07.

Dawson, A.J. (2004), 'Methodological reasons for not gaining prior informed consent are sometimes justified', BMJ, 329, 87.

Dean, M.E. (2004), 'The trials of homeopathy', KVC Verlag, Essen

Dean, M.E., Coulter, M.K., Fisher, P. et al. (2007), Reporting data on homeopathic treatments (RedHot): a supplement to CONSORT, Homeopathy, 96,1, 42-45.

Deeks, J.J., Dinnes, J., D'Amico, R. et al. (2003), 'Evaluating non randomised intervention studies', Health Technology Assessment, 7, 27.

Donnellan, P., Smyth, J., (2001), 'Informed consent and randomised controlled trials' Journal of the Royal College of Surgeons Edinburgh, 46, 100-102.

Downs, S.H., Black, N. (1998), 'The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions', J Epidemiol Community Health, 52, 377-384.

Dresser, R. (2002), 'The ubiquity and utility of the therapeutic misconception', Social philosophy and policy, 19, 2, 271-294.

Drew, P., Chatwin, J., Collins, S. (2001), 'Conversation analysis: a method for research into interactions between patients and health-care professionals', Health Expectations, 4, 58-70.

ECH Thesaurus on the European Committee for Homeopathy website
http://homeopathyeurope.org/pdf/homeothesaurusmulti.pdf accessed 1.1.08

Edwards, S.J.L., Lilford, R.J,. Braunholtz, D.A. et al. (1998), 'Ethical issues in the design and conduct of randomised controlled trials', Health Technology Assessment, 2, 15.

Edwards S.J.L., Braunholtz, D.A., Lilford, R.J. et al. (1999), 'Ethical issues in the design and conduct of cluster randomised controlled trials', BMJ, 1407-1409.

Edwards, P., Roberts, I., Clarke, M. et al. (2002), 'Increasing response rates to postal questionnaires: systematic review', BMJ, 324, 1183.

Eng, M., Taylor, L., Verhoef, M. et al. (2005), 'Understanding participation in a trial comparing cryotherapy and radiation treatment', Canadian Journal of Urology, 12, 2, 2607-2613.

Ernst E., Pittler M.H. (1998a), 'Efficacy of homeopathic arnica: a systematic review of placebo-controlled clinical trials'. Archives of Surgery, 133,11, 1187-90

Ernst, E., Barnes, J. (1998b), 'Are homoeopathic remedies effective for delayed-onset muscle soreness: a systematic review of placebo-controlled trials'. Perfusion,11, 4-8.

Ernst, E. (1999a), 'Classical homeopathy versus conventional treatments: a systematic review'. Perfusion, 12, 13-15.

Ernst, E. (1999b), 'Homeopathic prophylaxis of headaches and migraine? A systematic review', Journal of Pain & Symptom Management, 18, 5, 353-7.

Ernst, E. (2002), 'A systematic review of systematic reviews of homeopathy', British Journal of Clinical Pharmacy, 54,577-582.

Ernst, E., Pittler, M. (2006), 'Efficacy or effectiveness?'. Journal of Internal Medicine, 260, 5, 488–490.

Ettinger, B., Grady, D., Tosteson, A., et al. (2003), 'Effect of the Women's Health Initiative on women's decisions to discontinue post menopausal hormone therapy', Obstetrics & Gynaecology, 102, 6, 1225-1232.

Eyles, C. (2008), personal communication of work from unpublished PhD thesis, University of Southampton.

Faculty of Homeopathy (1999), 'Opportunities for Homeopathy within the New NHS'.

Feldman, B.M., Voda, A., Gronseth, E. (1985), 'The prevalence of hot flash and associated variables among perimenopausal women. Research in Nursing & Health, 8, 3, 261-8.

Firth J., (2007), 'Should you tell patients about beneficial treatments that they cannot have?', BMJ, 334, 826.

Fisher, P. (2008), 'Meta-analyses of homeopathy trials', Lancet, 371:985.

Fitter, M.J., Thomas, K.J., (1997), 'Evaluating complementary therapies for use in the National Health Service: 'Horses for courses' Part 1: The design challenge', Complementary Therapies in Medicine, 5, 90-93.

Fonnebo, V., Grimsgaard, S., Walach, H., et al., (2007), 'Researching complementary and alternative treatments – the gatekeepers are not at home', BMC Medical Research Methodology, 7, 7 doi10.1186/1471-2288-7-7.

Forbes, R.B., Colville, S., Swingler, R.J. (2004), 'Scottish Motor Neurone Disease Research Group. Frequency, timing and outcome of gastrostomy tubes for amyotrophic lateral

sclerosis/motor neurone disease--a record linkage study from the Scottish Motor Neurone Disease Register', Journal of Neurology, 251, 7, 813-7.

Francis T, Korns RF, Voight RB, et al. (1954), 'An evaluation of the 1954 poliomyelitis vaccine trials'. American Journal of Public Health, 45, 1-63.

Frass, M., Schuster, E., Muchitsch, I. et al. (2005), 'Bias in the trial and reporting of trials of homeopathy: A fundamental breakdown in peer review and standards?', Journal of Alternative and Complementary Medicine, 11, 5, 779-785.

Friese, K.H., Kruse, S., Lutdke, R., (1997), 'The homeopathic treatment of otitis media in children- comparison with conventional therapy'. International Journal of Clinical Pharmacology & Therapeutics, 35, 7, 296-301.

Gabbay, M., Thomas, J., (2004), 'When free condoms and spermicide are not enough: barriers and solutions to participant recruitment to community-based trials', Controlled Clinical Trials, 25, 4, 388-99.

Gartlehner, G., Hansen, R.A., Nissman, D. et al. (2006), 'Criteria for distinguishing effectiveness from efficacy trials in systematic reviews', Technical review 12 (Prepared by the RTI-International-University of North Carolina Evidence-Based Practice Center under Contract No.290-02-0016.) AHRQ Publication No.06-0046. Rockville, MD: Agency for Healthcare Research and Quality.

Gautier, J. (1983), 'Essai Therapeutique Comparitif De L'action De La Clonidine et Du Lachesis Mutans Dans Le Traitement des Bouffes et De Lia Chaleur De La Menopause. Universite de Bordeaux (thesis).

Goldacre, B. (2008), 'Meta-analyses of homeopathy trials – authors reply', Lancet, 371,985.

Grady, D. Herrington, G., Bittner, V. et al. (2002), 'Cardiovascular Disease Outcomes during 6.8 Years of Hormone Therapy: Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II)', Journal of the American Medical Association, 288, 49-57.

Green, J., Denham, A., Ingram, J. et al. (2007), 'Treatment of menopausal symptoms by qualified herbal practitioners: a prospective, randomized controlled trial', Family Practice, 24, 5, 468-474; doi:10.1093/fampra/cmm048

Greene, J.G. (1998), 'Constructing a standard climacteric scale', Maturitas, 29, 1, 25-31.

Hahnemann, S., (1811), 'Pure pharmaceutical science: first part', (German) Arnold, Dresden.

Halpern, S.D., Karlawish, J.H.T., Casarett, D.B. et al. (2003), 'Hypertensive patients' willingness to participate in placebo-controlled trials: implications for recruitment efficiency', American Heart Journal, 146, 6, 985-92.

Heaven B, Murtagh M, Rapley T, et al. (2006), 'Patients or research subjects? A qualitative study of participation in a randomised controlled trial of a complex intervention', Patient Education and Counseling, 62, 260-270.

Hewison, J., Haines, A. (2006), 'Overcoming barriers to recruitment in health research', BMJ, 333, 300-303.

Hewitt, C.E., Torgerson, D.J., Miles, J.V.N., (2006), 'Is there another way to take account of noncompliance in randomized controlled trials?' Canadian Medical Association Journal, 175, 347.

Hill, C., Doyon F. (1990), 'Review of randomized trials of homoeopathy'. Revue Epidemiologie Santé Publication, 38,139-147.

Hickey, M., Davis, D., Sturdee, D. (2005) Treatment of menopausal symptoms: what shall we do now?', Lancet, 366, 9483, 409-421.

Homer, C.S.E. (2002), 'Using the Zelen design in randomized controlled trials: debates and controversies'. Journal of Advanced Nursing, 38, 2, 200-207.

HM Treasury (2008). Budget 2008, Chapter C 23. Retrieved on 24.3.08

Hope S, Wager G, Rees M, (1998), 'Survey of British women's views on the menopause and HRT', Journal British Menopause Society, 4, 33-36.

Horton, R. (2005), 'The end of homoeopathy', Lancet, 366, 9487, 690.

House of Lords 6th Report (2000), Session 1999-2000. Select Committee on Science & Technology: Complementary & Alternative Medicine. London. The Stationery Office.

Hulley, S., Grady, D., Bush, T. et al. (1998), 'Randomised controlled trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women', JAMA, 280, 605 -613.

Huntley, A.L., Ernst, E. (2003), 'A systematic review of herbal medicinal products for the treatment of menopausal symptoms', Menopause, 10, 5, 465-476.

Jacobs, J., Herman P., Herron, K. et al. (2005), 'Homeopathy for menopausal symptoms in breast cancer survivors: a preliminary randomized controlled trial', Journal of Alternative & Complementary Medicine, 11, 1, 21-27.

Jacobson, J.S., Troxel, A.B., Evans, J. (2001), 'Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer', J Clinical Oncology, 19, 10, 2739-2745.

Jadad, A.R., (1998), 'Randomised controlled trials', BMJ books, London.

Jadad, A.R., Moore, R.A., Carol, D. et al. (1996), 'Assessing the quality of reports of randomised clinical trials: is blinding necessary?', Controlled Clinical Trials,17,1-12.

Jadad, A.R., Enkin, M.W. (2007), "Randomized controlled trials: Questions, answers and musings" BMJ books 2nd edition Blackwell publishing.

Jonas, W.B., Kaptchuk, T.J., Linde, K. (2003), 'A critical overview of homeopathy', Annals of Internal Medicine, 138, 5, 393-9.

Jonas, W.B., Linde K, Ramirez G. (2000), 'Homeopathy and rheumatic disease', Rheumatic Diseases Clinics of North America, 26, 117-123.

Junghans, C., Feder, G.S., Hemingway, H. et al. (2005), 'Recruiting patients to medical research: a double-blind randomised trial of 'Opt In' versus 'Opt Out' strategies', British Medical Journal, 331, 940-944.

Kaplan, B. (2001), 'The homeopathic conversation: the art of taking the case'. London, Natural Medicine Press.

Keenan, N.L., Mark, S., Fugh-Berman, A. et al. (2003), 'Severity of menopausal symptoms and use of both conventional and complementary/alternative therapies', Menopause, 10, 6, 507-515.

King, M., Nazareth, I., Lampe, F. et al. (2005), 'Conceptual framework and systematic review of the effects of participants and professionals' preferences in randomised controlled trials, Health Technology Assessment, 9, 35.

Kleijnen, J., Knipschild, P., Riet, G.R. (1991), 'Trials of homoeopathy', British Medical Journal, 302, 6782, 960.

Knight, D.C., Howes, J.B., Eden J.A. (1999), 'The effect of Promensil, an isoflavone extract, on menopausal symptoms', Climacteric, 2, 79-84.

Kronenberg, F. (1990), 'Complementary and Alternative Medicine for Menopausal Symptoms: A review of randomized controlled trials'. Annals of Internal Medicine, 137, 10, 805-814.

Kronenberg, F., O'Leary, C.J., McMahon, D. (1994), 'Alternative medicine for menopausal problems: results of a survey', Menopause 1, 171-2.

Lam, P.M., Cheung, G.W., Shek, D.T. et al. (2004), 'A randomised, placebo-controlled, crossover study of tibolone (Livial)', Menopause, 11, 4, 416-422.

Lancaster, G.A., Dodd, S.R., Williamson, P.R. (2004), 'Design and analysis of pilot studies: recommendations for good practice', Journal of Evaluation in Clinical Practice, 10, 2, 307-312.

Lagro-Janssen, T., Rosser, W.W., van Weel, C. (2003), 'Breast cancer and hormone replacement therapy: up to general practice to pick up the pieces' Lancet, 362, 414 – 415.

Last, J.M., (ed) (2001), A Dictionary of Epidemiology, Oxford University Press.

Lavelle, K., Todd, C., Campbell, M. (2008), ' Do postage stamps versus pre-paid envelopes increase response to patient mail surveys? A randomised controlled trial', BMC Health Services Research, 8, 113.

Lewsey J.D., Leyland, A.H., Murray, G.D., Boddy F.A., (2000), 'Using routine data to complement and enhance the results of randomised controlled trials' Health Technology Assessment, 4, 22.

Linde, K., Clausius, N., Ramirez, G. et al. (1997), 'Are the clinical effects of homeopathy placebo effects? A meta-analysis of randomised placebo-controlled trials', Lancet, 350, 834-843.

Linde, K., Melchart, D. (1998), 'Randomized controlled Trials of Individualized Homeopathy: A state of the art review', Journal of Alternative & Complementary Medicine, 4, 4, 371-388.

Linde, K., Vickers, A., Honduras, M. et al. (2001), Systematic reviews of complementary therapies – an annotated bibliography. Part 3: Homeopathy www.biomedcentral.com/1472-6882/1/4

Long, A.F., Mercer, G. (1999), 'Challenges in researching the effectiveness of complementary therapies', Journal of Contemporary Health, 8, 13-9.

Long, L., Ernst, E. (2001), 'Homeopathic remedies for the treatment of osteoarthritis: a systematic review'. British Homeopathic Journal, 90, 1, 37-43.

Loprinzi, C.L., Kugler, J.W., Sloan, J.A. et al. (2000), 'Venlafaxine in management of hot flashes in survivors of breast cancer: a RCT', Lancet, 356, 9247, 2059-63.

Loprinzi, C.L., Sloan, J.A., Perez, E.A. et al. (2002), 'Phase III evaluation of fluoxetine for treatment of hot flashes', J Clin Oncol, 20, 1578–1583.

Lutdke, R., Rutten, A.L.B. (2008), 'The conclusions on the effectiveness of homeopathy highly depend on the set of analyzed trials', Journal of Clinical Epidemiology, doi: 10.1016/j.jclinepi.2008.06.015

MacLehose, R.R., Reeves, B.C., Harvey, I.M. et al. (2000), 'A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies', Health Technology Assessment, 4, 34.

MacLennan, A., Lester, S., Moore, V. (2002), 'Oral oestrogen replacement therapy versus placebo for hot flushes' Cochrane Database of Systematic Reviews. 2001;(1):CD002978. http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD002978/frame.html

MacPherson, H., Thomas, K., Armstrong, B., de Valois, B., Relton, C., Mullinger, B., White, A., Flower, A., Scheid, V. (2008), 'Developing research strategies in complementary and alternative medicine'. Complementary Therapies in Medicine, 16, 359-362. http://dx.doi.org/10.1016/j.ctim.2008.08.001

Madsen, S.M., Mirza, S. Holm, K.L. et al. (2002), 'Attitudes towards clinical research amongst participants and nonparticipants', Journal of Internal Medicine, 251, 2, 156–168.

Maher, D., Schulz, K.F., Altman, D.G. (2001), 'The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials', Ann Intern Med,134, 657-62.

Manchandra, R.K. (2000), 'Cost effectiveness and efficacy of homeopathy in Primary Health Care units of Delhi – a study'. http://www.delhihomeo.com/paperberlin.html

Mapstone, J., Elbourne, D., Roberts, I. (2007), 'Strategies to improve recruitment to research studies'. Cochrane Database of Systematic Reviews Issue 2. Art nNo.:MR000013.DOI:10.1002/14651858.MR000013.pub3.

Marcus, R. (2007), 'Should you tell patients about beneficial treatments that they cannot have?', British Medical Journal, 334, 827.

Mays, N., Pope, C., (2000) 'Quality in qualitative health research' in Mays, N., & Pope, C., (eds). 'Qualitative research in healthcare', BMJ books, London.

McCarney, R., Warner J, Fisher P, Van Haselen R. (2003), 'Homeopathy for dementia'. Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD003803. DOI: 10.1002/14651858.CD003803.

McCarney, R., Linde K, Lasserson, T.J. (2004), 'Homeopathy for chronic asthma'. Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD000353. DOI: 10.1002/14651858.CD000353.pub2.

McColl, E., Jacoby, A., Thomas, L. et al. (2001), 'Design and use of questionnaires; a review of best practice applicable to surveys of health service staff and patients', Health Technology Assessment 5, 1.

McLeod, L., Barrett, J., Hewson, S. et al. (2004), 'Women's views regarding participation in a proposed randomized controlled trial of twin delivery', Journal of Obstetrics & Gynaecology Canada, 26,6, 575-9.

Medical Research Council (2000), 'A framework for development and evaluation of RCTs for complex interventions to improve health', www.mrc.ac.uk/complex_packages.html

Milazzo, S., Russell, N., Ernst, E. (2006), 'Efficacy of homeopathic therapy in cancer treatment'. European Journal of Cancer, 42, 3, 282-9.

Million women Study Collaborators (2003), 'Breast cancer and hormone-replacement therapy in the Million Women Study', Lancet, 362, 419-27.

Mishra, G., Hardy, R., Kuh, D., (2007), 'Are the effects of risk factors for timing of menopause modified by age? Results from a British birth cohort study', Menopause, 14, 4, 717-24.

Mowatt, G., Bower, D.J., Brebner, J.A., et al. (1997), 'When and how to assess fast changing technologies: a comparative study of medical applications of four generic technologies'. Health Technology Assessment, 1, 14.

MRC Clinical Trials Unit, http://www.ctu.mrc.ac.uk/TypesTrial.asp. accessed August 2007.

Nakash, R.A., Hutton, J.L., Jorstad-Stein, E.C. et al. (2006), 'Maximising response to postal questionnaires – A systematic review of randomised trials in health research', BMC Medical Research Methodology 6:5 doi10.1186/1471-2288-6-5

National Center for Complementary and Alternative Medicine (NCCAM). (2005), 'Whole medical systems: an overview', http://nccam.nih.gov/about/plans/fiveyear/ accessed 1.1.08

Ness, J., Aronow, W.S., Newkirk, E. (2005), 'Use of Hormone Replacement Therapy by Postmenopausal women after publication of the Women's Health Initiative Trial' The Journals of Gerontology, 60, 460-462.

Newton, K,M., Buist, D., Keenan, N.L. et al (2002), 'Use of alternative therapies for menopause symptoms: Results of a population based survey', American college of obstetricians and gynaecologists, 100, 1, 18-25.

NHS Centre for Reviews and Dissemination (CRD), (2002); Effective Health Care, 7, 3, 12 . http://www.york.ac.uk/inst/crd/ehcb.htm

Nicholl J.P., (1989), 'Outcome prediction in intensive care'. The Lancet, 11, 330-331.

Ockene, J.K., Barad, D.H., Cochrane, B.B. et al. (2005), 'Symptom experience after discontinuing use of estrogen plus progestin', JAMA 294,183-193.

Owen, D., (1990), 'An investigation into the Homoeopathic treatment of patients with irritable bowel syndrome'. British Homeopathic Congress, Windermere, UK. (also published as Lecoyte, T., Owen, D., Shepherd, H., Letchworth, A., Mullee, M. (1993), 'An investigation into the homeopathic treatment of patients with irritable bowel syndrome'. Proceedings of the 48th Congress of LMHI, Vienna, Austria, 251-258)

Owen, J.M., Green, B.N. (2004), 'Homeopathic treatment of headaches: a systematic review of the literature', Journal of Chiropractic Medicine, 3, 2, 45-52.

Partington, H. (2006), 'Membership survey'. Newsletter of the Society of Homeopaths Winter.

Paterson, C. (2004), 'Medication change Questionnaire' available at http://www.pms.ac.uk/mymop/files/MCQ_complete_users_pack.pdf

Paterson, C. (1996), 'Measuring outcomes in primary care: a patient generated measure, MYMOP, compared with the SF-36 health survey', BMJ, 312, 7037, 1016-20.

Patton, M.Q. (1990), Qualitative evaluation and research methods (2nd ed.). Newbury Park, CA: Sage.

Penotti, M., Elena, F., Modena, A.B. et al. (2003), 'Effect of Soy-Derived Isoflavones on Hot Flashes, Endometrial Thickness, and the Pulsatility Index of the Uterine and Cerebral Arteries' Obstetrical & Gynecological Survey, 58, 10, 673-674.

Pilkington, K., Kirkwood, G., Rampes, H. et al. (2005), 'Homeopathy for depression: a systematic review of the research evidence'. Homeopathy: Journal of the Faculty of Homeopathy, 94, 3, 153-63.

Pilkington, K., Kirkwood, G., Rampes, H.(2006), 'Homeopathy for anxiety and anxiety disorders: a systematic review of the research'. Homeopathy: the Journal of the Faculty of Homeopathy, 95, 3, 151-62.

Porter, M., Penney, G.C., Russell, E., et al. (1996), 'A population based survey of women's experience of the menopause', British Journal of Obstetrics & Gynaecology, 103, 1025-1028.

Prescott, R.J., Counsell, C.E., Gillespie, W.J., et al. (1999), 'Factors that limit the quality, number and progress of randomised controlled trials.', Health Technology Assessment, 3, 20.

Punch, K.F. (1998), 'Introduction to social research: qualitative & quantitative approaches' Sage publications, London.

Quella, S.K., Loprinzi, C.L., Barton, D.L., et al. (2000), 'Evaluation of soy phyto-estrogens for the treatment of hot flashes in breast cancer survivors', J Clin Oncol, 18,1068-74.

Rabin, R., de Charro, F. (2001), 'EQ-5D: a measure of health status from the EuroQol Group', Ann Med, 33, 5, 337-43.

Raftery, J., Roderick, P., Stevens, A. (2005), 'Potential use of routine databases in health technology assessment', Health Technology Assessment, 9, 20.

Relton, C., Weatherley-Jones, E. (2005), 'Homeopathy service in a NHS community menopause clinic: audit of clinical outcomes', Journal of the British Menopause society, 11, 2, 72-3.

Relton, C., (2004), 'A systematic review of homeopathy for PMS and the menopause' MSc dissertation, University of Sheffield.

Relton, C., Chatfield, K., Partington, H., et al. (2007), 'Patients treated by homeopaths registered with the Society of Homeopaths: a pilot study'. Homeopathy, 96, 87-89.

Relton, C., O'Cathain, A., Thomas, K.J. (2008), ''Homeopathy': Untangling the debate', Homeopathy, 97,152-155.

Relton, C., Smith, C., Walters, C., et al. (In press), 'Trial of adjunctive healthcare provided by a homeopath for Fibromyalgia Syndrome', Homeopathy.

Riley, D., Fischer, M., Singh, B. et al. (2001), 'Homeopathy and conventional medicine: an outcomes study comparing effectiveness in a primary care setting'. Journal of Alternative & Complementary Medicine 7, 2, 149-59.

Roberts, C., Torgerson, D. (1999), 'Baseline imbalance in randomised controlled trials', BMJ, 319, 185.

Robinson, E.J., Kerr, C.E.P., Stevens, A.J., et al. (2005), 'Lay publics understanding of equipoise and randomisation in randomised controlled trials', Health Technology Assessment, 9, 8.

Rodger, M.A., Makropoulos, D., Walker, M. et al. (2003), 'Participation of pregnant women in clinical trials: will they participate and why?' American Journal of Perinatology, 20, 2, 69-76.

Rojavin, M.A., Downs, P., Shetzline, M.A., et al. (2006), 'Factors motivating dyspepsia patients to enter clinical research', Contemporary Clinical Trials, 27, 2,103-11.

Rorty, R. (1983), Consequences of pragmatism. Minneapolis: University of Minnesota Press.

Rorty, R. (1990), 'Pragmatism as anti-representationalism. In J.P.Murphy (Ed), Pragmatism: From Peirce to Davidson (p1-6) Boulder, Colorado: Westview Press.

Rosenbaum, J.R., Wells, C.K., Viscoli, C.M. et al. (2005), 'Altruism as a reason for participation in clinical trials was independently associated with adherence', Journal of Clinical Epidemiology 58, 1109-1114.

Ross, P. (2008), 'Homeopathy in the UK' Lancet, 371, 9617, 985.

Ross, S., Grant A,, Counsell, C. et al. (1999), 'Barriers to participation in randomised controlled trials: a systematic review', Journal of Clinical Epidemiology, 52,12,1143-1156.

Rothwell, P.M. (2005), 'External validity of randomised controlled trials:"To whom do the results of this trial apply?"', Lancet, 365, 82 – 93.

Sackett, D.L., Richardson, W.S., Rosenberg, W., et al. (2000a), Evidence-based Medicine – How to Practice and Teach EBM, London, Churchill Livingstone (Second edition).

Saks, M., Allsop, J. (2007), 'Researching Health Qualitative, Quantitative and Mixed Methods' Sage Publications.

Salkeld, G., Quine, S., Cameron, I.D. (2004),'What constitutes success in preventative healthcare? A case study in assessing the benefits of hip protectors', Social Science and Medicine, 59, 1593-1601.

Scambia, G., Mango, D., Signorile, P.G. et al. (2001), 'Clinical effects of a standardised soy extract in postmenopausal women: a pilot study', Menopause, 7, 105-11.

Schellings, R., Kessels, A.G., ter Riet, G., et al. (1999), 'The Zelen design may be the best choice for a heroin-provision experiment' J Clin Epidmiol, 52, 6, 503-507.

Schellings, R., Kessels, A.G., ter Riet, G. et al. (2006), 'Randomized consent designs in randomized controlled trials: Systematic literature search', Contemporary Clinical Trials, 27, 4, 330-332.

Schwartz, D., Lellouch, J. (1967), 'Explanatory and pragmatic attitudes in therapeutic trials', Journal of Chronic Disease,20, 637-48.

Scott, A., (1998), 'Homeopathy as a feminist form of medicine', Sociology of health & illness, 20, 2, 191-214.

Seymour, J. (2001), 'As if by magic' New Scientist, 2292. http://www.newscientist.com/article/mg17022924.900-as-if-by-magic.html accessed 1.1.08

Shang, A., Huwiler-Muntener, K., Nartey, L. et al., (2005), 'Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy', Lancet, 366, 9487, 726-32.

Simile (2008), 'Homeopathy – 60 years in the NHS', Newsletter of the Faculty of Homeopathy.

Sloan, J.A., Loprinzi, C.L., Novotny, P.J., et al. (2001). 'Methodologic lessons learned from hot flash studies'. Journal of Clinical Oncology;19 (23):4280-4290.

Smith, C.A., (2003), 'Homoeopathy for induction of labour'. Cochrane Database of Systematic Reviews, Issue 4. Art. No.: CD003399. DOI: 10.1002/14651858.CD003399.

Snowdon, C., Elbourne, D., Garcia, J. (1999), 'Zelen randomization: attitudes of parents participating in a neonatal clinical trial'. Controlled Clinical Trials, 20, 149-171.

Song, F., Altman D.G., Glenny, A.M. et al. (2003), 'Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses', BMJ, 326, 472 – 477.

Spence, D.S., Thompson, E.A., Barron, E.A., (2005), 'Homeopathic treatment for chronic disease; a 6 – year, university hospital outpatient observational study', Journal of Alternative & Complementary Medicine, 11, 5, 793-8.

Speroff, L., Symons, J., Kempfert, N. (2000), 'The effect of varying low dose combinations of norethindrone acetate and ethinyl estradiol on the frequency and intensity of vasomotor symptoms', Menopause, 7, 6, 383-390.

St Germain, A., Peterson, C.T., Robinson, J.G. (2001), 'Isoflavone rich or isoflavone poor soy protein does not reduce menopausal symptoms during 24 weeks of treatment', Menopause, 8, 17-26.

Stearns, V., Isaacs, C., Rowland, J. et al. (2000), 'A pilot trial assessing the efficacy of paroxetine hydrochloride (Paxil) in controlling hot flashes in breast cancer survivors', Annals of Oncology, 11, 17-22.

Stearns V, Ullmer L, Lopez JF, et al. (2002), 'Hot flushes', Lancet, 360,1851-1861.

Stearns, V., Beebe, K.L., Iyengar, M. et al. (2003), 'Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial', JAMA, 289, 2827–2834.

Stone, D.H. (1993), 'Design a questionnaire', BMJ, 307, 1264-1266.

Sullivan, I.M., D'Agostino, R.B. (2003), 'Robustness and power of analysis of covariance applied to ordinal scaled data as arising in randomized controlled trials', Statistics in Medicine, 22, 1317-1334.

Sutton, A.J., Abrams, K.R., Jones, D.R., et al., (1998), 'Systematic reviews of trials and other studies', Health Technology Assessment, 2,19.

Swayne, J. (1989), 'Survey of the use of homoeopathic medicine in the UK health system'. Journal of Royal College of General Practitioners, 503-506.

Teixeira, M.Z., (1999),'Similitude in modern pharmacology', British Homeopathic Journal 88,112-120.

Thomas, K.J., Nicholl, J.P., Coleman, P. (2001), 'Use and expenditure on complementary and alternative medicine in England – a population based survey', Complementary Therapies in Medicine, 9, 1, 2-11.

Thomas, K., Strong, P. (2003), 'Complementary medicine service in a community clinic for patients with symptoms associated with the menopause: Outcome study and service evaluation'. Final report unpublished. Medical Care Research Unit, University of Sheffield. UK.

Thomas, K., Coleman, P. (2004), 'Use of complementary or alternative medicine in a general population in Great Britain. Results from the National Omnibus Survey'. Journal of Public Health 26, 2, 152-157.

Thomas, K.J., MacPherson, H., Thorpe, L., et al. (2006), 'Randomised controlled trial of a short course of traditional acupuncture compared with usual care for persistent non-specific low back pain', BMJ, 333, 623.

Thompson, E.A., Reilly, D., (2002), 'The homeopathic approach to symptom control in the cancer patient: a prospective observational study'. Palliative Medicine,16, 3, 227-33.

Thompson, E.A., Reilly, D. (2003), 'The homeopathic approach to the treatment of symptoms of oestrogen withdrawal in breast cancer patients: A prospective observational study' Homeopathy, 92,131-134.

Thompson, E.A., Montgomery, A., Douglas, D. et al. (2005), 'A pilot randomised double blind placebo-controlled trial of individualised homeopathy for symptoms of oestrogen withdrawal in breast cancer survivors'. Journal of Alternative & Complementary Medicine, 11,1, 13-20.

Thompson, E.A., Thompson, T.D. (2006), 'Placebo or non-specific effects: what are the unique ingredients in homeopathy?', The Homeopath 25, 3, 82-3.

Thompson, E.A., Mathie, R.T., Baitson, E.S. et al. (2008), 'Towards standard setting for patient-reported outcomes in the NHS homeopathic hospitals', Homeopathy, 97,114-121.

Thompson, T., (2006), 'Homeopathy – what are the active ingredients? An exploratory study using the UK MRC's framework for the evaluation of complex interventions', BioMedCentral http://www.biomedcentral.com/1472-6882/6/37

Thorpe K.E., Zwarenstein M., Oxman A.D. et al (2009), 'A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers' Journal of Clinical Epidemiology 62, 464-475.

Torgerson, D.J., Roland, M. (1998), 'Understanding clinical trials: what is Zelen's design?', BMJ, 316, 606-607.

Torgerson, D.J., Torgerson, C.J., (2008), Designing randomised trials in health, education and the social sciences: an introduction, Palgrave Macmillan.

Torgerson, D.J., Sibbald, B. (1998), 'Understanding controlled trials: what is a patient preference trial?', BMJ, 316: 360.

Truog, R.D., Robinson, W., Randolph, A. et al. (1999), 'Is informed consent always necessary for randomised controlled trials?', New England Journal of Medicine, 340, 804-7.

Tunis, S.R., Stryer, D.B., Clancy, C.M., (2003), 'Practical clinical trials: Increasing the value of clinical research for decision making in clinical and health policy', JAMA 290, (12), 1624-1632.

Upmalis, D.H., Lobo, R., Bradley, L. (2000), 'Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women', Menopause, 7, 4, 236-242.

Utian,W.H. (2005), 'Psychosocial and socioeconomic burden of vasomotor symptoms in menopause; a comprehensive review', Health and quality of life outcomes, http://www.hqlo.com/content/3/1/47.

Van Hootegem, H., (2007), 'Can homeopathy learn something from psychoanalysis?', Homeopathy, 96, 2, 108-112.

Van Patten, C.L., Olivotto, I.A., Chambers, G.K. et al. (2002), 'Effect of soy phytoestrogens on hot flashes in postmenopausal women with breast cancer: a RCT', Journal of Clinical Oncology, 99, 389-94.

Vandenbroucke, J.P. (1997), 'Homoeopathy trials: going nowhere', Lancet, 350, 824.

Verhoef, M., Lewith, G., Ritenbaugh, C. (2004), 'Whole systems research: Moving forward', Focus on alternative complementary therapies, 9, 87-90.

Vickers, A., (2000), 'Evaluation of specific and non-specific effects in homeopathy: feasibility study for a randomised trial', British Homeopathic Journal, 89, S1, S48-49.

Vickers, A.J., Smith, C., (2006), 'Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes', Cochrane Database of Systematic Reviews, Issue 3. Art. No.: CD001957. DOI: 10.1002/14651858.CD001957.pub3.

Villarruel, A.M., Jemmott, L.S., Jemmott, J.B. et al. (2006), 'Recruitment and retention of Latino adolescents to a research study: lessons learned from a randomized clinical trial', Journal for Specialists in Pediatric Nursing, 11, 4, 244-50.

Wall, M., Wheeler, S. (1996), 'Benefits of the placebo effect in the therapeutic relationship', Complementary Therapies in Nursing & Midwifery, 2, 6, 160-3.

Watson, J., Wise, L., Green, J., (2006). 'Recent trends in the prescribing of hormone therapy for the menopause, tibolone, raloxifene and oral bisphosphonates in postmenopausal women in the UK', Proceedings of the UK Society for Social Medicine 50th Annual Scientific Meeting. Poster presentation.

Weatherley-Jones E, Nicholl J, Thomas KJ, et al. (2004a), 'A randomised, controlled, triple-blind study of the efficacy of homeopathic treatment for Chronic Fatigue Syndrome trial', Journal of Psychosomatic Research, 56,189-197.

Weatherley-Jones, E., Thompson, E.A., Thomas, K.T., (2004b), 'The placebo-controlled trial as a test of complementary and alternative medicine: observations from research experience of individualised homeopathic treatment', Homeopathy, 93,186-189.

West Kent PCT Homeopathy consultation (2007): http://www.westkentpct.nhs.uk/home-page/what-we-do/ppi/public-consultations/homeopathy-consultation/ accessed 16.8.07

West, J., Wright, J., Tuffnell, D. et al. (2005), 'Do clinical trials improve quality of care? A comparison of clinical processes and outcomes in patients in a clinical trial and similar patients outside a trial where both groups are managed according to a strict protocol', Quality & Safety in Health Care, 14, 175-178.

Wiesenauer, M.L., Ludtke, R. (2000), 'A meta-analysis of the homeopathic treatment of pollinosis with Galphimia glauca', British Homeopathic Journal, 89, S1, S52.

Wiles, R., Heath, S., Crow, G. et al. (2005), 'Informed consent in social research: A literature review', ESRC National Centre for Research Methods. NCRM methods review NCRM/001.

Williams, J.G., Cheung, W.Y., Cohen, D.R. et al. (2003), 'Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment', Health Technology Assessment, 7, 26.

Williamson, J., White, A., Hart, A., et al. (2002), 'A randomised controlled trial of reflexology for menopausal symptoms', BJOG: An International Journal of Obstetrics & Gynaecology, 109, 9, 1050-1055.

Wilson, R.A. (1966), Feminine Forever, New York. M. Evans and Company Inc.

Winter, R., (1991), 'Homoeopathy: medicine or magic?', BMJ, 302, 120.

Witt, C., Keil, T., Selim, D. et al., (2005a), 'Outcome and costs of homeopathic and conventional treatment strategies: a comparative cohort study in patients with chronic disorders'. Complementary Therapies in Medicine, 13, 2, 79-86.

Witt, C.M., Lutdke, R., Baur, R., et al. (2005b), 'Homeopathic medical practice: Long-term results of a cohort study with 3981 patients', BMC Public Health, 5:115.

White, C. (2002), 'Second long term HRT trial stopped early', BMJ, 325, 987.

World Health Organization (1996), Research on the menopause in the 1990's. WHO Technical Report Series 866. Geneva: World Health Organization Press.

Writing Group for the Women's Health Initiative Investigators, (2002),' Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial, JAMA, 288, 321-33.

Zelen, M. (1979), 'A new design for randomized clinical trials' New England Journal of Medicine, 300, 1242-5.

Zelen, M. (1990), 'Randomized consent designs for clinical trials: an update', Statistics in medicine, 9, 645-56.

Zoellner, Y.F. (2002), Global Health Economics, Solvay Pharmaceuticals, PO Box 220, D-30002, Hannover, Germany.