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

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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 Medicine's 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 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).

1.2.5 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

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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).
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)

1.3.2 Homeopathy and clinical trials

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

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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 (Lüdtke & 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).
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.” (AcademyHealth, 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

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 intercurrent 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. 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.

2.3 The current debate: homeopathy in the NHS

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

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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>
<thead>
<tr>
<th>Phase I</th>
<th>Context, paradigms, philosophical understanding and utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II</td>
<td>Safety status</td>
</tr>
<tr>
<td>Phase III</td>
<td>Comparative effectiveness</td>
</tr>
<tr>
<td>Phase IV</td>
<td>Component efficacy</td>
</tr>
<tr>
<td>Phase V</td>
<td>Biological mechanisms</td>
</tr>
</tbody>
</table>

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 effectiveness.

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\(^6\) 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.

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 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’

---

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).
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.

2.7.4 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….“. 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**

<table>
<thead>
<tr>
<th>II</th>
<th>Allows the complexity and proper functioning of the intervention</th>
</tr>
</thead>
</table>

### 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**

<table>
<thead>
<tr>
<th>I</th>
<th>Pragmatic randomised controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Allows the complexity and proper functioning of the intervention</td>
</tr>
</tbody>
</table>

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:

- 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 & Lüdtke, 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

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 & Lüdtke, 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:

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- Systematic reviews of individualised homeopathy trials (2/25)
- Comparative systematic reviews of homeopathy (1/25)

\(^9\) Dean’s review (2004) was peer reviewed for his PhD thesis rather than peer reviewed for publication.
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 & Lüdtke, 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, Lüdtke & 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>
<thead>
<tr>
<th>Type</th>
<th>Author/ year</th>
<th>Title</th>
<th>Conclusion</th>
<th>CCTs*</th>
<th>RCTs**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic reviews of all clinical trials</td>
<td>Kleijnen et al. 1991</td>
<td>Trials of homeopathy</td>
<td>“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”</td>
<td>39</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Hill &amp; Doyon 1990</td>
<td>Randomised trials of homeopathy</td>
<td>“results do not provide acceptable evidence that homoeopathic treatments are effective”</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Dean 2004</td>
<td>Trials of homeopathy 1940 - 1995</td>
<td>“the majority of trials reported positive effects, either significant or strong trends, regardless of the type of control or homeopathy that was trialled”</td>
<td>52</td>
<td>153</td>
</tr>
<tr>
<td>Systematic reviews of Classical/Individualised homeopathy</td>
<td>Ernst 1999a</td>
<td>Classical homeopathy vs conventional treatments</td>
<td>“It is concluded that at present the relative efficacy of homeopathic remedies is not known”</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Linde &amp; Melchart 1998</td>
<td>RCTs of individualised homeopathy</td>
<td>“the results of the available randomized trials suggest that individualised homeopathy has an effect over placebo.”</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>Systematic review of placebo controlled trials</td>
<td>Linde et al. 1997</td>
<td>Are the clinical effects of homeopathy placebo effects? A meta analysis of placebo controlled trials</td>
<td>“the results of our meta-analysis are not compatible with the hypothesis that the clinical effects of homeopathy are completely due to placebo. However, we found insufficient evidence from these studies that homeopathy is clearly efficacious for any single clinical condition”</td>
<td>0</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>Cucherat et al. 2000</td>
<td>Evidence for clinical efficacy of Homeopathy</td>
<td>“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”</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Comparative systematic review of allopathic and homeopathy</td>
<td>Shang et al. 2005</td>
<td>Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of allopathy vs homeopathy</td>
<td>random or quasi random assignment</td>
<td>0</td>
<td>110 vs 110</td>
</tr>
<tr>
<td>placebo RCTs</td>
<td></td>
<td></td>
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<tr>
<td>Author/ year</td>
<td>Title</td>
<td>Purpose</td>
<td>CCT</td>
<td>RCT</td>
<td>Conclusion</td>
</tr>
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<tr>
<td>Altunc et al. 2007</td>
<td>Homeopathy for childhood &amp; adolescence ailments</td>
<td>To assess the evidence of any type of therapeutic or preventative intervention testing homeopathy for childhood and adolescence ailments</td>
<td>0</td>
<td>16</td>
<td>“…not convincing enough for recommendations in any condition”</td>
</tr>
<tr>
<td>Barnes et al. 1997</td>
<td>Homeopathy for post operative ileus: a meta-analysis</td>
<td>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</td>
<td>0</td>
<td>6</td>
<td>“There is evidence that homeopathic treatment can reduce the duration of ileus after abdominal or gynaecologic surgery”</td>
</tr>
<tr>
<td>Coulter et al. 2006</td>
<td>Attention-deficit hyperactivity disorder/ hyperkinetic disorder</td>
<td>To evaluate the evidence for the efficacy and safety of homoeopathy for treating ADHD or HKD</td>
<td>0</td>
<td>4</td>
<td>“The efficacy of homoeopathy for ADHD/HKD is uncertain”</td>
</tr>
<tr>
<td>Ernst &amp; Pittler 1998a</td>
<td>Are homeopathic remedies effective for delayed onset muscle soreness?</td>
<td>To determine whether homeopathic remedies are more effective than placebo in reducing the signs and symptoms of DOMS</td>
<td>5</td>
<td>3</td>
<td>“Evidence does not support the hypothesis that homeopathic remedies… are more efficacious than placebo”</td>
</tr>
<tr>
<td>Ernst &amp; Barnes 1998b</td>
<td>Efficacy of homeopathic arnica</td>
<td>To systematically review the clinical efficacy of homeopathic arnica</td>
<td>4</td>
<td>4</td>
<td>“The claim that homeopathic arnica is efficacious beyond a placebo effect is not supported by rigorous clinical trials”</td>
</tr>
<tr>
<td>Ernst 1999b</td>
<td>Homeopathic prophylaxis of headaches &amp; migraines</td>
<td>To evaluate the clinical trials, testing the efficacy of homeopathy for the prophylaxis of migraine and headaches</td>
<td>0</td>
<td>4</td>
<td>“Trial data. do not suggest that homeopathy is effective in the prophylaxis of migraine or headache beyond a placebo effect”</td>
</tr>
<tr>
<td>Jonas et al. 2000†</td>
<td>Homeopathy and rheumatic disease</td>
<td></td>
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<tr>
<td>Long &amp; Ernst 2001</td>
<td>Homeopathic remedies for the treatment of osteoarthritis</td>
<td>To assess all RCTs of homeopathy in the treatment of patients with OA</td>
<td>0</td>
<td>4</td>
<td>“There appeared to be a positive trend towards the effectiveness of combination homeopathic preparations … the small number of trials preclude firm conclusions”</td>
</tr>
<tr>
<td>McCarney et al.</td>
<td>Homeopathy for dementia</td>
<td>To evaluate the effectiveness and safety profile of homeopathically prepared medications used</td>
<td>0</td>
<td>1</td>
<td>“There were no studies that fulfilled the criteria for inclusion”</td>
</tr>
<tr>
<td>Year</td>
<td>Authors</td>
<td>Study Title</td>
<td>Study Objective</td>
<td>Study Results</td>
<td></td>
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<td>--------</td>
<td>--------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>2003</td>
<td>McCarn et al. 2004</td>
<td>Homeopathy for chronic asthma</td>
<td>The objective of this review was to assess the effects of homeopathy in people with chronic stable asthma.</td>
<td>0/6 “There is not enough evidence to reliably assess the possible role of homeopathy in asthma”</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Milazzo et al. 2006</td>
<td>Efficacy of homeopathic therapy in cancer treatment</td>
<td>To evaluate the effectiveness of any type of homeopathic therapy in the treatment of patients with cancer</td>
<td>1/4 “Although the evidence was encouraging, there was insufficient evidence to support the use of homeopathy”</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Owen &amp; Green 2004</td>
<td>Homeopathic treatment of headaches</td>
<td>To review trials relating to the homeopathic treatment of tension type, cervicogenic and migraine headache</td>
<td>0/4 “Insufficient evidence to support or refute the use of homeopathy”</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Pilkington et al. 2005</td>
<td>Homeopathy for depression</td>
<td>To evaluate the effectiveness, including safety and patient satisfaction of homeopathy for the treatment of depression</td>
<td>0/3 “Evidence for the effectiveness of homeopathy in depression is limited because of a lack of high-quality trials”</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Pilkington et al. 2006</td>
<td>Homeopathy for anxiety and anxiety disorders</td>
<td>To conduct a systematic review of the clinical research evidence on homeopathy in the treatment of anxiety and anxiety disorders</td>
<td>?/8 “RCTs report contradictory results, are underpowered or provide insufficient details of methodology. (Several observational studies reported positive results)”</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Smith 2004</td>
<td>Homeopathy for induction of labour</td>
<td>To determine the effects of homeopathy for third trimester cervical ripening or induction of labour</td>
<td>0/2 “There is insufficient evidence to recommend the use of homeopathy as a method of induction”</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Vickers &amp; Smith 2006</td>
<td>Homeopathic Oscillococcinum for preventing and treating influenza like syndromes</td>
<td>To determine whether homeopathic Oscillococcinum or similar medicines are more effective than placebo in the preventions and treatment of influenza and influenza like syndromes</td>
<td>0/7 “Though promising the data were not strong enough to make a general recommendation to use Oscillococcinum”</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Wiesenauer 2000</td>
<td>A meta-analysis of the homeopathic treatment of pollinosis with Galphimia glauca</td>
<td>To assess the efficacy of homeopathically prepared Galphimia glauca compared with placebo in the treatment of pollinosis</td>
<td>4/7 “Significant superiority of Galphimia glauca over placebo is demonstrated”</td>
<td></td>
</tr>
</tbody>
</table>

† No information available
* CCTs Controlled Clinical Trials
** RCTs Randomised controlled trials
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 and as published describe 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. 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
‘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 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.

### 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 “recurring 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.

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13 Oestrogen and estrogen are different spellings of the same hormone.
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\textsuperscript{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 Inhibitors (SSRIs) such as Venlafaxine, 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

\textsuperscript{14} The Royal College of Obstetricians & Gynaecologists (http://www.rcog.org.uk/ accessed 22.8.08) do not produce ‘Menopause’ guidelines
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 thrombotic 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-
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’ (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. 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.

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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)
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 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

<table>
<thead>
<tr>
<th>III</th>
<th>Have findings that can be generalised to the ‘with need’ population</th>
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<tbody>
<tr>
<td>IV</td>
<td>Produce short and long term outcomes</td>
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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 al., 2003). 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

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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
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).

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 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 premenstrual 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 these treatments suggested that they were no better than placebo. However, a small number of CAM treatments 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

\(^{19}\) Flash is the American equivalent of the English term ‘flush’
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

<table>
<thead>
<tr>
<th>I</th>
<th>Pragmatic RCTs</th>
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<tr>
<td>II</td>
<td>Allow the complexity and proper functioning of intervention</td>
</tr>
<tr>
<td>III</td>
<td>Have findings that can be generalised to the ‘with need’ population</td>
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<tr>
<td>IV</td>
<td>Produce short and long term outcomes</td>
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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.