Chapter 4
The patient perspective on clinical trial participation

4.1 Introduction

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

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

4.1.1 Aim & objectives

The aim of this chapter is to identify key criteria for an appropriate pragmatic RCT design from the individual patient’s perspective on participating in clinical trials. The objectives of this chapter are to:

- explore the literature as to why patients do enter clinical trials
4.2. Why do patients enter clinical trials?

4.2.1 Opting in
As a result of the Data Protection Act of 1998 and NHS Information Governance (www.connectingforhealth.nhs.uk), researchers cannot approach patients directly to participate in research, instead the researcher must approach the current (or last treating) clinician who (if they believe the request is appropriate) may then approach the patient to ask if the patient wishes to participate in the research. Only those patients who respond positively to this request may then be contacted by the researcher. In short, patients have to ‘opt in’ to rather than ‘opt out’ of research. The next step for the researcher is to obtain ‘Informed Consent’ from those patients who express an interest in ‘opting in’¹. Participating in a clinical trial is thus viewed as being contingent to an individual patient’s relationship with their current clinician. However, RCTs are designed to help patients collectively in the future rather than each individual patient now, this section explores some of the literature as to why individual patients do enter clinical trials.

4.2.2 Methods
There has been no systematic literature review published on why patients do enter clinical trials. Rather than perform an extensive literature search of this area, this thesis examines a commonly held assumption as to why patients enter clinical trials: that patients enter clinical trials because they are motivated by altruism² (the selfless concern for the welfare of others which is seen as a virtue in Western culture). For example the International Committee of Medical Journal Editors states that:

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

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

¹ Research indicates that an ‘opt out’ system produces higher recruitment rates and a more representative population (Junghans, 2005)
² In the genome and biobank debates, altruism is sometimes described as ‘genetic solidarity’. 
spectrum and ‘patients’ at the other end. Heaven et al. reports that those who identified themselves as ‘patients’ were more likely to describe their reasons for participation as personal benefit rather than altruism. The assumption that the main reason why patients enter clinical trials is altruism is explored through a review of the relevant literature reporting empirical findings.

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

4.2.3 Characteristics of the articles included

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

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

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

In understanding the literature it is helpful to categorise the types of benefits reported. King et al., (2000) offer a helpful typology which was applied to the 11 included studies (Table 4.1).

This typology identifies three potential types of benefit from being a research participant:

- **Direct benefit** from receiving the intervention under study (e.g. money, access to particular treatment) – available to study patients who are allocated to the study intervention

- **Indirect benefit** from participating in a clinical trial (e.g. academic medical setting, close monitoring) – available to all study patients

- **Aspirational or altruistic benefit** related to what will be learned as a consequence of the research.
Table 4.1 (Patients and clinical trials: reasons for participation) reports those studies which used closed questions first and then those studies which used open questions.

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

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

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

Rosenbaum et al. (2005) sought to determine whether altruism as a reason for participation in research is independently associated with adherence to a medical regimen in a clinical trial and found that under half (45.7%) of participants provided at least one altruistic reason for participation and a fifth (20.6%) gave an altruistic reason as their only reason for participation. Halpern et al. (2003) reported the most commonly cited motivations for participation in a hypothetical trial were ‘personal’: personal health benefit (40%), access to care (12%), money (6%) (i.e. ‘direct’ or ‘indirect’ benefits). The most commonly cited non personal motivations cited were: altruism (37%) and to contribute to scientific knowledge (14%) (which King et al. describes as ‘aspirational or altruistic benefits’). Rodger et al. 2003 reported that the most
<table>
<thead>
<tr>
<th>Author Year (Country)</th>
<th>Title of article</th>
<th>Type of patient</th>
<th>Clinical condition</th>
<th>Number of patients</th>
<th>Questions</th>
<th>Reasons for participation</th>
<th>Main reason for participation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criscione et al. 2003 (USA)</td>
<td>Informed Consent in a clinical trial of a novel treatment for rheumatoid arthritis</td>
<td>Participants</td>
<td>Rheumatoid arthritis</td>
<td>30</td>
<td>Closed</td>
<td>Being in this trial gives me hope &amp; to help other patients with RA (99%)</td>
<td>Direct benefit</td>
</tr>
<tr>
<td>Madsen et al. 2002 (Denmark)</td>
<td>Attitudes towards clinical research amongst participants and non participants</td>
<td>Participants &amp; non Participants</td>
<td>Cancer trials</td>
<td>41/47</td>
<td>Closed</td>
<td>Access to new drug Being closely monitored To help future patients</td>
<td>Direct benefit</td>
</tr>
<tr>
<td>McLeod et al. 2004 (Canada)</td>
<td>Women’s views regarding participation in a proposed RCT of twin delivery</td>
<td>Participants in a hypothetical trial</td>
<td>Pregnant mothers with a known twin gestation</td>
<td>64</td>
<td>Closed</td>
<td>Most common agreement to participation was altruism (n=28)</td>
<td>Altruism</td>
</tr>
<tr>
<td>Rojavin et al. 2006 (USA)</td>
<td>Factors motivating dyspepsia patients to enter clinical research</td>
<td>Participants</td>
<td>Dyspepsia</td>
<td>247</td>
<td>Closed</td>
<td>1. To receive treatment 2. Get skilled professional care 3. Altruism</td>
<td>Direct &amp; indirect benefit</td>
</tr>
<tr>
<td>Gabbay &amp; Thomas 2004 (UK)</td>
<td>When free condoms and spermicide are not enough: barriers and solutions to participant recruitment to community-based trials</td>
<td>Participants &amp; non participants</td>
<td>Condom &amp; additional spermicide trial</td>
<td>303</td>
<td>Closed</td>
<td>Considering the research important (85%) Wanting to help the researchers (70%) Having time to help (62%) Getting free condoms &amp; lubricant (56%)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Study</td>
<td>Title</td>
<td>Participants</td>
<td>Disease/Intervention</td>
<td>Sample Size</td>
<td>Recruitment Status</td>
<td>Recruitment-Centric Reasons</td>
<td>Type of Benefit</td>
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<tr>
<td>Eng et al. 2005 (Canada)</td>
<td>Understanding participation in a trial comparing cryotherapy and radiation treatment</td>
<td>Participants &amp; non participants</td>
<td>Prostate cancer</td>
<td>11</td>
<td>Open</td>
<td>Participants principally in the hope of getting cryotherapy treatment</td>
<td>Direct benefit</td>
</tr>
<tr>
<td>Heaven et al. 2006 (UK)</td>
<td>Patients or research subjects? A qualitative study of participation in a randomised controlled trial of a complex intervention</td>
<td>Participants</td>
<td>RCT of decision support tools</td>
<td>31</td>
<td>Open</td>
<td>The majority hoped to benefit to some degree from participation &amp; a primary desire to contribute to advancing medical practice and the wellbeing of others</td>
<td>Not reported</td>
</tr>
<tr>
<td>Rosenbaum et al. 2005 (USA)</td>
<td>Altruism as a reason for participation in clinical trials was independently associated with adherence</td>
<td>Participants</td>
<td>Estrogen for stroke</td>
<td>475</td>
<td>Open</td>
<td>45.7% gave at least one altruistic reason for participation 20.6% only gave an altruistic reason for participation</td>
<td>Direct &amp; indirect benefit</td>
</tr>
<tr>
<td>Villarruel et al. 2006 (USA)</td>
<td>Recruitment and retention of Latino adolescents to a research study: lessons learned from a RCT</td>
<td>Participants</td>
<td>Reducing HIV sexual risk behaviour</td>
<td>106</td>
<td>Open</td>
<td>Four main facilitator patterns emerged: peer/family support, program incentives, commitment and a desire to help</td>
<td>Not reported</td>
</tr>
<tr>
<td>Rodger et al. 2003 (USA)</td>
<td>Participation of pregnant women in clinical trials; will they participate and why?</td>
<td>Participants in a hypothetical trial</td>
<td>Pregnant women</td>
<td>50</td>
<td>Open</td>
<td>Potential benefit to fetus (68%) Benefit to personal health 27% Altruism (5%)</td>
<td>Direct &amp; indirect benefit</td>
</tr>
<tr>
<td>Halpern et al. 2003 (USA)</td>
<td>Hypertensive patients willingness to participate in placebo controlled trials: implications for recruitment efficiency</td>
<td>Participants in a hypothetical trial</td>
<td>Hypertensive patients</td>
<td>126</td>
<td>Open</td>
<td>Personal health benefits (40%) Helping other patients (37%) Contributing to scientific knowledge (14%) Access to care (12%) Money (6%)</td>
<td>Direct benefit</td>
</tr>
</tbody>
</table>
important determinants of pregnant women’s willingness to participate in a hypothetical clinical trial were: potential benefit to fetus (68%), benefit to personal health (27%), and altruism (5%).

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

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

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

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

The evidence from this literature review is congruent with the hypothesis that the primary motive or aim of the individual patient is to receive the best treatment for themselves for their
condition (X). Another way of testing this hypothesis is to examine why patients do not enter clinical trials. If patients do not enter clinical trials because they believe that they will not receive the best treatment for themselves now – then this would support the above hypothesis. The next section asks the question ‘why don’t patients enter clinical trials’?

4.3. Why don’t patients enter clinical trials?

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

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

4.3.3 Location of research
The majority of studies (n=39) were conducted in cancer patients and in the USA (n=48). Only 10 studies from the UK were included. As was mentioned earlier, since the bulk of the US healthcare system is not free at point of delivery, patients often participate in research in order to obtain free treatment – this is much less the case in the UK and Europe. In order to see if the location of the research affected the reported findings, information from 26 studies that were conducted in the USA (refs 7 – 33 & 79-80 in Ross et al.) was removed to obtain information from studies conducted in countries where healthcare is free at point of delivery (Europe & Canada), but similar results were found.
Table 4.2  Barriers to patient participation in RCTs (Ross et al., 1999)

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

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

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

Pragmatic trials are by their current definition pragmatic in purpose (in their aim to inform healthcare decisions within routine practice) and usually pragmatic in the manner in which the intervention is modelled, but do they model the trial processes in a pragmatic way? If clinical trials could replicate the processes of routine healthcare then the results of such trials would be
more generalisable to patients in routine healthcare and thus more pragmatic. This thesis suggests that the fifth key criterion for appropriate clinical trial design from the patient’s perspective is that trials aim to replicate the processes of routine healthcare wherever possible (Box 4.1).

Box 4.1 Key Criterion V

| V | Aim to replicate the processes of routine healthcare |

4.4 Informed Consent for trials: an examination of current practice

At this point, although a key criterion for appropriate clinical trial design has been identified, it is not clear what it would mean for trial to ‘replicate the processes of routine healthcare’. In order to explore what this might mean, this section starts to explore the current information and consent processes of clinical trials from the perspective of the individual patient. The formal procedures used to recruit patients into clinical trials in the NHS are known as Informed Consent, and are regarded as an important ethical safeguard for patients entering clinical trials by the World Medical Association’s Helsinki Declaration http://www.wma.net/e/policy/b3.htm accessed 19.8.08. This section describes ‘Informed Consent’ - the current NHS bureaucratic procedures for informing patients about research and seeking and obtaining their consent to participate in a clinical trial; and then goes on to examine current practice and experience from the perspective of the individual patient.

4.4.1 National Research Ethics Services

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

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

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

“Part one should provide brief and clear information on the essential elements of the study: the condition or treatment under study; the voluntary nature of involvement; what will happen during and after the trial, what treatment may be withheld; the participant’s responsibilities; the potential risks, inconvenience or restrictions, benefits, and the alternative(s).

Part two should contain additional information on factors such as confidentiality and data protection, communication with the GP, indemnity and compensation, and publication. This should be read and understood before the participant decides whether they want to participate.”


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

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

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

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

4.4.5 Consent form
The consent form consists of five statements that the patient must read and confirm their assent to by ticking a box.
1. ‘I confirm that I have read and understand the information sheet dated….. version….. For the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily’
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at…. I give my permission for these individuals to have access to my records.
4. I agree to my GP being informed of my participation in the study
5. I agree to take part in the above study.

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

4.4.6 Discussion

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

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

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

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

4.5. Informed Consent procedures: the patient’s perspective

The existing Health Services Research literature provided clarity as to the reasons why patients do not participate in clinical trials, but no solutions. So in the search for an appropriate solution the following approach was taken. Social psychology attempts to explain patterns of behaviour
in a general sense and one’s psychological development in, and interaction with, a social environment. ‘Social constructionism’ is a popular method used in social psychology, which focuses on uncovering the ways in which individuals and groups participate in the creation of their perceived social reality. Within constructionist thought, ‘social constructs’ are concepts or practices that appear normal and obvious to those who accept them, but in reality are artefacts or inventions of a particular culture or society. Political scientists such as Brekke & Sirnes (2006) have suggested that Informed Consent is such a construct and that the construct of Informed Consent functions both as a ‘regulatory tool’ and signifier of ‘normal’ and responsible scientific conduct (Brekke & Sirnes, 2006). This thesis adopts the position that ‘Informed Consent’ is an example of a social construct, a construct which describes socially and legally acceptable ways of accessing patients and recruiting them for the purposes of research.

4.5.1 Deconstruction

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

4.5.2 Information

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

A. ‘There is a healthcare/treatment option that may benefit you’ - This type of information is given in routine healthcare at the appropriate point for the patient – i.e. when there is the possibility that they will get it. This information raises expectations (especially for ‘new’
treatments) and thus from the research viewpoint introduces the possibility of expectation bias, and disappointment/resentful demoralisation bias (Brewin & Bradley, 1989) if the preferred allocation is not given. To quote a NHS consultant: “It is no good offering access to … care then …making people wait for weeks with no certainty about who will or won’t be seen” (Health Service Journal, 2007, ‘Doing well by depression’ Supplement 6, p16).

Types of information B-F are peculiar to the context of research but rarely found in routine healthcare:

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

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

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

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

3 One of my supervisors told me the following anecdote that they had been told by a Canadian surgeon participating in a workshop on designing clinical trials. The Canadian surgeon reported explaining a trial to a potential participant and the fact that there was uncertainty about the best treatment. At the end of the discussion the surgeon asked the patient if he had any questions. “Yes” said the patient, “Can you refer me to a surgeon who does know what is the best treatment for me?”
knows that they may not get the treatment they want, and the clinician may not be able to give
the patient the treatment that they want (if the clinician has a treatment preference). Information
as to the random allocation to groups may reinforce the clinician’s uncertainty regarding the
best treatment for the patient, and potentially disempowering the clinician and altering the
therapeutic relationship.
Knowledge of uncertainty as to treatment allocation may bias the results through
disappointment or demoralisation affecting the reporting of both patient reported and objective
outcomes (Torgerson & Sibbald 1998). Uncertainty as to treatment allocation rarely occurs in
routine healthcare⁴ and is a significant barrier to clinical trial recruitment (Ross et al., 1999).
In 1982, Appelbaum et al. coined the term the ‘Therapeutic misconception’. This is the
mistaken but commonly held belief of study participants that therapy and research are
governed by the same primary goal: to advance the individual’s patient’s interests (Dresser,
2002). One example of this is the fact that patients generally find randomisation (an
experimental artifice) difficult to understand and apply to their treatment or their clinician’s
decision making behaviour as due to the therapeutic misconception, patients generally believe
or like to believe that their clinician knows best.

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

**F. ‘You may receive dummy treatment’** – this informs the patient that in participating in the
research they will be in a situation where there is the random possibility of dummy treatment –
a placebo. Information about masked placebo may result in patients wondering if they are being
deceived, and thus, when reporting outcomes, question the accuracy of their own perceptions
of their health and symptoms. Patients in routine healthcare however are almost never told that
they may receive a dummy treatment⁵.

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

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⁴ One example of uncertainty as to treatment allocation in routine healthcare is the
phenomenon of postcode ‘lottery’ - where the location of an address determines the treatment
which is available. This is perceived as unfair and part of the rationale for the existence of NICE
is to rectify the unfairness of the chance in the postcode ‘lottery’.

⁵ Placebos are not overtly prescribed in routine healthcare but there is a long, widespread and
ongoing tradition of clinicians giving placebos – treatments that will not directly address the
health needs of the patient but are given in such a way that it is implied that they will e.g.
antibiotics for viral infections.
This thesis argues that from the patient's (rather than trial participant's) experience the types of information that are needed are those that are provided in routine healthcare and each type of information is required when needed rather than multiple types of information all provided at a single point in time. In routine healthcare, patients are given each piece of information when they need it and as they need it. From the patient’s perspective a key criterion for appropriate clinical trial design is that information is appropriate to the patient being a patient (rather than a research participant) (Box 4.2)

**Box 4.2 Key Criterion VI**

| VI | Have ‘patient’ appropriate information |

4.5.3 Consent

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

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

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

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

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

**D. Consent to treatment outcome uncertainty** - consent to enter into a state or situation of uncertainty as to which is the best treatment or the effectiveness or safety of treatment.
<table>
<thead>
<tr>
<th>Research term</th>
<th>Consent</th>
<th>Relationship or context</th>
<th>Information</th>
<th>Impact/ possible bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Patient</td>
<td>Be treated</td>
<td>Clinician/ patient relationship</td>
<td>‘There is a treatment and it may benefit you’</td>
<td>Expectation of benefit – Expectation bias</td>
</tr>
<tr>
<td><strong>B</strong> Participant</td>
<td>Be a research participant</td>
<td>Researcher/ participant in research relationships</td>
<td>‘There is research about..’</td>
<td>Amplification of effect and biases of A, C, D, E, F</td>
</tr>
<tr>
<td><strong>C</strong> Collect data/ perform test</td>
<td>Be observed</td>
<td>Observer/ observed relationship</td>
<td>‘We want to observe you..’</td>
<td>‘I am special’ Hawthorne effect</td>
</tr>
<tr>
<td><strong>D</strong> Equipoise</td>
<td>Treatment outcome uncertainty</td>
<td>State of uncertainty.. not knowing?</td>
<td>‘We are not sure which treatment is best....’</td>
<td>‘They don’t know which treatment is best for me..’ Increases patients sense of uncertainty, disempowers clinician &amp; alters therapeutic relationship</td>
</tr>
<tr>
<td><strong>E</strong> Random allocation</td>
<td>Have no control over allocation (allocation uncertainty)</td>
<td>Relationship of player to game Fate, chance</td>
<td>‘We are going to play a game of chance’</td>
<td>‘I might not get what I want’ Disappointment bias ‘My patient might not get the treatment I think is best’ Refusal to recruit</td>
</tr>
<tr>
<td><strong>F</strong> Masked Placebo</td>
<td>Possibility of dummy treatment</td>
<td>State of uncertainty Relationship of player to game Fate, chance</td>
<td>‘You may receive dummy treatment’</td>
<td>‘Am I better/worse or just imagining it?’ ‘I feel deceived’</td>
</tr>
</tbody>
</table>
E. Consent to allocation uncertainty (chance) - This consent involves the patient giving up direct control (patient choice) and indirect control (nominated decision maker e.g. GP). This type of consent is similar to entering a game of chance.

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

Table 4.3 summarise the consents sought in current NRES Informed Consent procedures. In routine healthcare, patients consent to situations and relationships as and when they arise, but Informed Consent for clinical trials generally requests multiple types of consent to be given at a single time point. Consents B – F do not generally occur in routine healthcare, and it is obvious that each of these types of consent may impact on the patient, particularly consents D, E & F which each introduce an element of uncertainty into the healthcare experience for the patient.

As with information, from the patient’s perspective, the types of consent that are appropriate are those sought/given in routine healthcare, as and when required and not multiple consents at a single point in time. From the patient’s perspective a key criterion for appropriate clinical trial design is that consent is appropriate to the patient being a patient (rather than a research participant) (Box 4.3)

Box 4.3 Key Criterion VII

| VII | Have 'patient' appropriate consent |

4.6. Discussion: the patient experience

4.6.1 Recruitment

Recruitment and Informed Consent are often seen as immutable processes that happen before the trial proper begins, but it is perhaps more realistic to say that a trial begins the moment that a patient is treated differently from how they are in routine healthcare; this usually starts with recruitment. Hewison & Haines (2006) state that “Recruitment procedures are part of the science, not an administrative add-on”. During recruitment, information can impact on the expectations, behaviour, experiences and clinical outcomes of patients even though consent has not been given e.g. hearing that ‘there is a ‘new’ treatment invariably leads patients and clinicians to think that the new treatment is better in some way than existing treatments. Because of the tension between the participant’s right to refuse and the motivation of the researcher to achieve a high response rate, researchers have used various ways to increase the possibility that participants obtain direct or indirect personal benefit from participating in
trials e.g. ensuring that treatment is only available within the trial\(^6\), offering financial or material rewards, building patient’s expectations about the efficacy of the intervention. These incentives or inducements could be seen as a form of coercion that impacts on the voluntary nature of research participation (Wiles et al., 2006) and as such could be viewed as unethical. Researchers (e.g. Chalmers, 1995; Torgerson & Torgerson, 2008) have stated that patients frequently fare better in trials than out, regardless of whether they receive a ‘beneficial’ intervention. Indeed Chalmers (1995) has cited an indirect benefit as a rationale for trial participation as “patients receiving treatments as participants in such trials seem to fare better than apparently comparable patients receiving the same treatments outside trials”; however West et al. (2005) suggest there is no difference in clinical outcomes between patients in a clinical trial and patients receiving protocol driven care and that the benefits of improved clinical care that have previously been associated with being in a trial may be explained by the use of clear clinical protocols.

4.6.2 The ethics of NRES Informed Consent in clinical trials

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

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

Truog et al. (1999) argue that the requirements for consent in clinical trials are too rigorous, and that the same level of disclosure is not required in routine practice. It appears that the NRES Informed Consent procedures (as well as much of the literature on why patients don’t participate in trials) have been written on the implicit premise that patients participate in research for altruistic reasons. If patients do participate from altruism then this supposedly validates the NRES Informed Consent ‘participant’ (instead of ‘patient’) discourse.

4.7. Summary

\(^6\) In paediatric oncology most children with cancer are enrolled in research because the community of practice agreed to develop an all-encompassing research agenda in order to make progress against the disease (Kolata 1999 in King et al. 2000)
This chapter has argued that the research processes begin as soon as patients are told about the existence of the clinical trial. A small number of individuals may be motivated primarily by altruism to enter trials – to be research participants, however the majority of individuals enter clinical trials in order to obtain the best healthcare possible – to be patients – and are motivated primarily by direct/indirect benefit. This chapter has described how ICH-GCP states subjects should be informed of all aspects of the trial that are “relevant to the subject’s decision to participate”, but NRES Informed Consent Guidance (section 4.4.3) operationalises ‘Informed Consent’ as full rather than “relevant” information – recommending the inclusion of information about the “essential elements of the study,… what treatment may be withheld”. This means that patients are given full information about random allocation to treatment group (before randomisation) and all the different types of treatments they may be allocated to, including treatment as usual or no treatment; information which although ‘full’ is not relevant to patients primary status and identity as patients.

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

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

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

**Box 4.4 Key Criteria V- VII**

<table>
<thead>
<tr>
<th>V</th>
<th>Replicate the processes of routine healthcare</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI</td>
<td>Have ‘patient’ appropriate information</td>
</tr>
<tr>
<td>VII</td>
<td>Have ‘patient’ appropriate consent</td>
</tr>
</tbody>
</table>
The same argument holds true for recruiting clinicians. It is acknowledged that for clinicians there is a potential conflict of interest between what is good for the current patient and what is good for future patients (Donnellan & Smyth, 2001).

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

Chapter 5

The Health Services Research perspective on clinical trials

5.1 Introduction

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

Box 5.1 Key criteria I – VII

<table>
<thead>
<tr>
<th>I</th>
<th>Pragmatic randomised controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Allow for the complexity &amp; proper functioning of intervention</td>
</tr>
<tr>
<td>III</td>
<td>Have findings that can be generalised to the 'with need' population</td>
</tr>
<tr>
<td>IV</td>
<td>Produce short and long term outcomes</td>
</tr>
<tr>
<td>V</td>
<td>Aim to replicate the processes of routine healthcare</td>
</tr>
<tr>
<td>VI</td>
<td>Have 'patient' appropriate information</td>
</tr>
<tr>
<td>VII</td>
<td>Have 'patient' appropriate consent</td>
</tr>
</tbody>
</table>
This chapter addresses the challenge of identifying key criteria for appropriate trial design from the perspective of academics who construct, conduct and critique clinical trials – the perspective of the academic discipline of Health Services Research (HSR)⁷, a “multidisciplinary field of scientific investigation” (AcademyHealth, 2002).

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

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

5.2. The HSR perspective

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

5.2.2 Internal & external validity
The validity of the causal inferences drawn from scientific studies such as the RCT can be divided into two types– internal validity and external validity. ‘Internal validity’ can be defined as - the observed state of affairs within the study is free from bias and confounding. ‘External validity’ can be defined as - the observed state of affairs within the study applies outside the study and the results are therefore externally generalisable. RCTs are constructed to have high internal validity (by avoiding allocation and selection bias) and there are checklists to assess the internal validity of clinical trials (Jadad et al., 1996). Awareness of internal validity issues is widespread and is now addressed through many journals requiring trial reports to use the

⁷ The HSR perspective could also perhaps be described as the collective patient perspective, since society (patients collectively) funds universities.
CONsolidated Standards of Reporting Trials (CONSORT) reporting guidelines (www.consort-statement.org); these guidelines include a checklist of items to include when reporting a randomised trial and includes ‘flow of participants through each stage’ and ‘number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. These items enable the reader to directly assess the internal validity of the trial. Internal validity is a prerequisite for external validity as the results of a flawed trial are invalid and the question of its external validity becomes irrelevant.

Due to its perceived inherent strong internal validity, the (well conducted) RCT is widely perceived as the gold standard research design for evaluating effectiveness, and systematic reviews and meta-analyses of RCTs are regarded as the top of the evidence base hierarchy (Sackett et al., 2000a).

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

Box 5.2 Key Criterion VIII

| VIII External as well as internal validity |

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8 Another explanation is that clinicians know that treatments have variable effectiveness depending on the characteristics of the patients, thus they ask ‘do the results of this trial apply to this patient?’ How to design studies to help clinicians treat individual patients rather than populations of patients is an important question that has not been addressed in this thesis. However, this issue is addressed in homeopathy. Homeopathy has always assessed the effect of every homeopathic remedy on individual patients using Human Pathogenetic Trials (HTPs) (also known as homeopathic ‘provings’). The aim of HPTs is to identify those patient characteristics which will predispose those patients to respond well to particular homeopathic medicines e.g. patients who report feeling hot, hungry and itchy respond better to the homeopathic remedy ‘sulphur’ than those who do not report feeling hot, hungry and itchy. HTPs have been conducted for several thousand homeopathic medicines and are still being conducted today worldwide.
The external validity of trial design is not just an important issue from an HSR perspective. The external validity of RCT design has been identified as a critical issue in all three areas so far explored in this thesis: reviews of systematic reviews of homeopathy (chapter 2), reviews of interventions for hot flushes (chapter 3), and the patient perspective (chapter 4).

5.2.3 External validity and the HTA methodology programme

Unlike internal validity, there is no well known or commonly used method or set of tools or checklist\(^9\) for assessing the external validity of RCTs. In order to understand the relationship between appropriate trial design and external validity more thoroughly, and to identify further key criteria for appropriate trial design, a review of the methodological issues which affect the external validity of RCTs was required. The HSR literature on the external validity of RCTs is vast, so this thesis examined a rigorous, up to date body of writing which covers this area, the NHS R&D Health Technology Assessment (HTA) programme; this provides the most appropriate body of high quality literature on trials and trial methods that relate to the purposes of NHS clinical research methods. The HTA programme was set up in 1993 following the publication of the first NHS R&D strategy, which aimed to create a research system that provided high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. The majority of HTA trials are pragmatic NHS based RCTs which aim to produce information about outcomes that have high external and internal validity. Within the broader HTA programme there is a specific HTA ‘Methodology’ programme which specifically aims to identify and answer important methodological questions relevant to HTA, however other areas of the HTA programme also cover methodological questions. Since this chapter is from the current HSR perspective then the literature of the NHS R&D Health Technology Assessment (HTA) programme provides an appropriate body of high quality literature on trials and trial methods that relate to the purposes of NHS clinical research methods.

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

5.3.1 Review aim

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

\(^9\) There are two published checklists for external validity briefly discussed in chapter 9 (Rothwell, 2005; Downs, 1998)
5.3.2 Review methods

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

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

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

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

- Description & implications of recruitment issues
- Analysis of the reasons for the recruitment issues
- Discussion and/or testing of possible solutions to recruitment issues.
5.3.3 Description & implications of recruitment issues
Failure to recruit and unrepresentative study populations were the two main recruitment issues described.

A. Failure to recruit: All 17 reports mention the fact that many trials fail to recruit sufficient numbers. Of 114 multi centre MRC & HTA funded trials which ran between 1994 and 2003, less than a third recruited their original target within the time originally specified, and a third had extensions in attempts to recruit the required number of participants (Campbell M., 2007). Failure to recruit has implications for both the cost, and the validity/reliability/comparability of the results of the RCT. Recruiting sufficient numbers is thus an important key criterion for valid RCT design from the current HSR perspective (Box 5.3).

Box 5.3 Key Criterion IX

| IX | Recruit sufficient numbers |

B. Unrepresentative study population
All 17 reports stated that many trials fail to recruit trial populations that are representative of the reference population with the trial populations often having a different clinical, demographic and psycho-social profile to the eligible treatment population as a whole. Participants recruited to trials tend to be younger, more likely to be male, white/Caucasian and healthier than the potential pool of patients from which they are recruited (Bartlett et al., 2005) and older, female, ethnic, patients with multiple co-morbidities tend to be excluded. The exclusion from trials of those people who are likely to be in need of an intervention can result in disparities between the reference population and the ‘trials’ population, thus compromising trial generalisability. For example an analysis of 27 trials of statins for use for secondary prevention of coronary heart disease (CHD) revealed that those aged 65+ formed nearly two thirds of the ‘with need’ population but only one fifth of the trial populations (Bartlett et al., 2005). Measures of absolute effectiveness are vital for the analyses of benefit, harm and cost effectiveness. If the different population groups are not adequately represented and effectiveness is variable, then such analyses may be severely biased or skewed. Study populations should be representative of all patients currently being treated for the condition (Bartlett et al., 2005; Britton et al., 1998). In the USA appropriate representation of women and ethnic minorities in publicly funded trials is required by legislation. However in the UK inclusivity in research is not currently formally promoted. Thus from an HSR perspective a key criterion for appropriate clinical trial design is that the recruited population is representative of the reference population (Box 5.4)

Box 5.4 Key Criterion X

| X | Recruited population is representative of the reference population |
5.3.4 Reasons for recruitment issues

Half the reports discussed the reasons for recruitment issues (Campbell M., 2007; Prescott et al., 1999; MacLehose et al., 2000; Britton et al., 1998; MacLehose et al., 2000; Robinson et al., 2005; Ashcroft et al., 1997; Edwards et al., 1998). There was widespread acknowledgment that the reasons for the failure to recruit and the lack of representativeness of those recruited were complex and discussions concerning the reasons for recruitment issues fell into two overlapping areas – A. Preferences and B. Informed consent.

A. Preferences

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

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

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

Box 5.5 Key Criterion XI

| XI | Patient and practitioner preferences remain unaltered |
B. Informed consent
Two broad areas were discussed in relation to Informed Consent – understanding the information and the ethics of randomisation and uncertainty.

Understanding the information
Many reports identified a range of issues regarding Informed Consent (Prescott et al., 1999; Robinson et al., 2005; Ashcroft et al., 1997; Edwards et al., 1998; MacLehose et al., 2000). Many patients do not fully understand the information given to them during consent consultations (Ashcroft et al., 1997); in particular most patients do not understand the meaning or implications of certain key abstract concepts ( equipoise, randomisation), integral to giving consent to participate in an RCT (Ashcroft et al., 1997; Edwards et al., 1998; Prescott et al., 1999; Robinson et al., 2005). Many people participating in research are unaware of the differences between participating in a research study and receiving routine treatment in the clinical setting. Most lay patients believe that doctors in RCTs DO know best, and transfer their expectation that their doctor will act in their (the patient’s) best interest from a clinical setting to a research setting – this is known as the *therapeutic misconception*. Additionally, most patients believe that it is unacceptable to use chance to decide upon what treatment they will receive (Robinson et al., 2005) and many patients are unwilling to be randomised (MacLehose et al., 2000). Ashcroft et al., (1997) suggests that many RCTs run the risk of being unethical in practice, even if they seem to be ethical in principle due to patients being unable to understand the principles and purposes of the RCT. Thus from an HSR perspective a key criterion for appropriate clinical trial design is that the procedures of Informed Consent are not a barrier to recruitment (Box 5.6).

Box 5.6 Key Criterion XII

| XII | Informed Consent procedures are not a barrier to recruitment |

The ethics of randomisation and uncertainty
The ethics of randomisation, the impact of uncertainty and the disparity between the assumptions underlying trial design and the assumptions about trial design in the publics understanding were highlighted in several reports (Edwards et al., 1998; Ashcroft et al., 1997). Edwards et al., describes uncertainty as ‘an underpinning issue’ of the ethical arguments which bear on RCTs and discusses both the Kantian and the Utilitarian perspectives on the ethics of participation in RCTs, concluding that fully informed consent for all patients is an unobtainable ideal.
What is seen as 'equipoise' from the researcher’s perspective is seen as 'uncertainty' from the patient’s perspective. The existence of equipoise justifies the use of randomisation in the research design, however providing information as to 'randomisation' (and hence 'equipoise'/uncertainty') acts a barrier to participation and brings ethical issues to bear.

5.3.5 Identifying key criteria
The aims of this methods review were to identify and understand the nature of the methodological issues relating to the external validity of RCTs by searching and assessing the literature of the HTA literature, and to derive key criteria for appropriate trial design from the HSR perspective.

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

**Box 5.7 Key Criteria VIII - XII**

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

5.4 Possible solutions to methodological issues

Having identified both the key methodological issues from the HSR perspective, and the five key criteria for appropriate clinical trial design from the HSR perspective, it is now time to address the second aim of this review – to examine possible solutions to the methodological issues. This examination will be conducted using not just those key criteria derived from the current HSR perspective (VIII – XII) but will incorporate a broader HSR perspective by using all 12 key criteria from all four domains: the intervention, the condition, the patient and the science of HSR (I – XII). This section assesses the ability of each ‘possible solution’ to meet all 12 key criteria from this broader perspective.
HTA reports which discussed possible solutions to RCT recruitment issues fell into two types; firstly, those that discussed using data from non randomised studies instead of RCTs, and secondly, those that discussed using alternative RCT designs. Six HTA reports examined ways of circumventing recruitment issues to RCTs by asking whether either routine clinical data or non randomised study data could be used instead of data from RCTs. Four reports (Raftery et al., 2005; Bartlett et al., 2005; Lewsey et al., 2000; Williams et al., 2003) looked at clinical databases that collect routine data and two published reports (Britton et al., 1998; MacLehose et al., 2000) looked at data from non randomised studies.

5.4.1 Database and non randomised studies

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

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

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

### Box 5.8 Key Criteria I - XII

I Pragmatic randomised controlled trial  
II Allows the complexity & proper functioning of intervention  
III Findings generalisable to ‘with need’ population  
IV Produce short and long term outcomes  
V Aim to replicate the processes of routine healthcare  
VI ‘Patient’ appropriate information  
VII ‘Patient’ appropriate consent  
VIII External as well as internal validity  
IX Recruit sufficient numbers  
X Recruited population is representative of the reference population
The use of data from non-randomised studies and/or routine clinical databases meets many of the key criteria including the majority of the key criteria from the current HSR perspective – IX (Recruit sufficient numbers), X (Recruited population is representative of the reference population), XI (Patient and practitioner preferences unaltered), IV (Produce short and long term outcomes) and XII (Informed consent procedures are not a barrier). However, studies which use data from routine clinical databases or non-randomised study data lack randomised data and thus are vulnerable to the possibility of confounding by unknown prognostic factors, and thus have poor internal validity and thus key criterion VIII (External as well as internal validity) is not met.

5.4.2 Alternative RCT designs

Researchers have proposed and used a variety of designs to overcome a range of problems with RCTs and there is a vast literature reporting these designs. A review of this literature is outside the scope of this thesis; however there is an HTA report\(^\text{11}\) (MacLehose et al., 2000) which identified ten study designs that have been proposed to address one or more of the problems often found with standard RCTs. The rest of this chapter examines these 10 RCT designs in more detail. All ten designs (as well as the standard pragmatic RCT design) are reported in Table 5.1. This table describes the rationale (advantages) and disadvantages of each design, and states which key criteria are met by the design.

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

Hybrid designs

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

\(^{11}\) This report aimed to investigate the association between methodological quality and the magnitude of estimates of effectiveness derived from RCTs and quasi-experimental and observational studies (QEOs).
Each of the hybrid designs results in two sets of data – data from those who are randomly allocated and data from those who are not randomly allocated.

**The Comprehensive cohort study design**
The first hybrid design is the Comprehensive cohort study design (described by Francis, 1954; Olschewski, 1985; Olschewski, 1992; in MacLehose et al., 2000) which was created to address the issue of patients having a preference against giving consent to random allocation to treatment. This design starts with a cohort of patients who are then asked to consent to randomisation; all patients are followed up, irrespective of whether or not they consented to randomisation. At the end of the study there are two sets of data - observational data from those who did not consent to randomisation and experimental data from those who did consent to randomisation. This is a pragmatic RCT design (I), which allows the complexity & proper functioning of the intervention (II), enables the production of long term outcomes (IV), where patient & practitioner preferences are unaltered (XII) and where informed consent is not a barrier (XII). However this design does not replicate the processes of routine healthcare because some of the patients are asked to consent to random allocation to treatment prior to randomisation. This design also does not increase the number of patients recruited to the randomised arm(s).

**Patient preference trial**
The second Hybrid design is the Patient preference trial (Brewin & Bradley, 1989) which was created to address the issue of patient preferences for certain treatments over other treatments. This design allows patients with strong preferences to choose their preferred treatment rather than be randomly allocated to treatment. This design differs from the Comprehensive cohort study design in that patient’s preferences are elicited and their stated preferences then determines which group each patient is allocated to, whereas group allocation in the Comprehensive cohort study design is determined by the patients preference for/against random allocation to treatment. It is interesting to note that the trial design is called ‘Patient preference trial’ rather than ‘Participant preference trial’, thus acknowledging the importance of treating individuals in trials primarily as ‘patients’ rather than ‘research participants’. This is a pragmatic randomised controlled trial design (I) which allows the complexity & proper functioning of the intervention (II) where patient preferences are unaltered (XI). However this design has no advantages over the current problematic standard pragmatic RCT design as it does not increase the number of patients recruited to the randomised arm(s).
Table 5.1  Standard pragmatic and alternative RCT designs

<table>
<thead>
<tr>
<th>Trial design</th>
<th>Rationale for the design</th>
<th>Key Criteria fully met</th>
<th>Disadvantages of the design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard pragmatic RCT (randomisation post consent)</td>
<td>To obtain measures of effectiveness from a trial design with high internal validity</td>
<td>I, II</td>
<td>Poor recruitment rates, patient and clinician treatment experiences altered, poor generalisability, lack of long term outcomes, unrepresentative recruited population, poor external validity, ethical issues and informed consent a barrier to recruitment</td>
</tr>
<tr>
<td>Comprehensive cohort study design</td>
<td>Addresses the issue of patient preferences against consent to random allocation to treatment</td>
<td>I, II, IV, XI, XII</td>
<td>Does not increase the number of patients recruited to the randomised arm(s)</td>
</tr>
<tr>
<td>Patient preference trial</td>
<td>Allows patients with strong preferences to choose between treatments offered</td>
<td>I, II</td>
<td>Does not increase the number of patients recruited to the randomised arm(s)</td>
</tr>
<tr>
<td>Two stage trial</td>
<td>To separate the physiological from the psychological effects of treatment</td>
<td>I, II</td>
<td>Does not increase the number of patients recruited to the randomised arm(s)</td>
</tr>
<tr>
<td>Clinician preferred trial</td>
<td>Allows clinicians with preferences to choose between treatments for their patients</td>
<td>I, II</td>
<td>Does not increase the number of patients recruited to the randomised arm(s)</td>
</tr>
<tr>
<td>Randomised play-the-winner trial</td>
<td>To increase the number of patients receiving the superior treatment during the trial</td>
<td>II</td>
<td>Quasi randomisation therefore poor internal validity</td>
</tr>
<tr>
<td>Randomised discontinuation trial</td>
<td>To minimise the number of patients exposed to placebo</td>
<td>None</td>
<td>Withdrawal of treatment from treatment responders increase drop out and presents ethical issues Uses placebo – therefore not a pragmatic RCT design</td>
</tr>
<tr>
<td>Change to open label</td>
<td>Offers patients the possibility of unmasked treatment within the trial</td>
<td>None</td>
<td>Proxy outcome – time until patient requests open label Uses placebo – therefore not a pragmatic RCT design</td>
</tr>
<tr>
<td>Placebo run-in trial</td>
<td>Increased efficiency by weaning out non compliers in first phase</td>
<td>None</td>
<td>Uses placebo – therefore not a pragmatic RCT design</td>
</tr>
<tr>
<td>Double randomised consent design</td>
<td>To address issue of obtaining informed consent prior to randomisation</td>
<td>I, II, III, (V,VI,VII), VIII, IX, X, XI, XII</td>
<td>If TAU then patients told they have been randomly allocated to no treatment Ethical issues Statistical analysis issues</td>
</tr>
<tr>
<td>Single randomised consent design</td>
<td>To address issue of obtaining informed consent prior to randomisation</td>
<td>I, II, III, V, VI, VII, VIII, IX, X, XI, XII</td>
<td>Ethical issues Statistical analysis issues</td>
</tr>
</tbody>
</table>
Two stage trial
The third hybrid design is the Two stage trial which was designed to separate and quantify the physiological effects of a treatment from the psychological or placebo effects of treatment. Eligible patients are randomised into one of two study arms: ‘option’ or ‘random’. In the ‘option’ arm, patients are offered a free choice between treatments being evaluated, but if they have no preference then they are asked to consent to be randomised to one of the treatments. In the ‘random’ arm patients are asked to consent to be randomised to either treatment. The ‘option’ arm collects randomised and non randomised data and the ‘random’ arm collects randomised data only. There are obvious difficulties; explaining this trial design to patients, recruiting patients with preferences to this design, and analysing the results from of the six arms. There have been no published trials that have used this design. This is a pragmatic trial design (I). However this design does not increase the number of patients recruited to the randomised arm(s) and thus has no advantages over the current problematic standard pragmatic RCT design.

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

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

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

Randomised discontinuation trial
The second RCT variant is the ‘Randomised discontinuation trial’ which is a two phase trial design. The rationale for this design is to attempt to assess the clinical activity of a drug while minimising the number of patients exposed to placebo treatment. Phase I is an open phase in which all patients are given the treatment. At the end of Phase I, the effects of the treatment are reviewed and recruited patients are divided into ‘responders’ and ‘non responders’. ‘Non responders’ includes patients who suffer adverse health effects, non compliers and non improvers. Non-responders are excluded from Phase II of the trial in which responders are randomised into placebo and verum groups. This design decreases the heterogeneity of the randomly assigned population, resulting in increased statistical power with smaller patient numbers.
This is a non pragmatic RCT design which has been rarely used. The drop out rate of those responders who initially responded to treatment and are then randomised to placebo is likely to be high as it is unlikely that patients who are responding to treatment would then consent to the possibility of being randomly allocated to placebo. This design is unlikely to receive NHS ethical approval as it means that clinicians have to withdraw treatment from patients who appear to have benefited if they are randomised into the placebo group. The randomised discontinuation trial does not appear to facilitate any of the key criteria for appropriate trial design.

Change to open label design
The third RCT variant is the Change to open label design. This is a placebo RCT design which begins in the conventional manner but allows patients to change to open (as opposed
to masked) treatment when they want to. The outcome measure is the time until a patient requests open treatment, analysed using survival methods. There is no published report of an evaluation using this design. It is unclear how well knowledge of ‘time until patient request open treatment’ can serve as a proxy marker for ‘patient satisfaction with their progress’ and thus can inform clinical decision making. As the design uses placebo it is not a pragmatic RCT design and therefore does not meet key criterion I or facilitate any of the other key criteria.

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

**Randomised Consent Designs**
The fifth and sixth RCT variants are both Randomised Consent Designs - the **Double Randomised Consent Design (DRCD)** and the **Single Randomised Consent Design (SRCD)**. Both designs seek to address issues around obtaining informed consent prior to randomisation. The randomised consent design was originally proposed by Marvin Zelen, as a way of maximising recruitment by only seeking consent to participate from those already randomised to the intervention arm, thus helping overcome the discomfort for physician and patient of explaining equipoise and acknowledging uncertainty (Zelen, 1979). It was hoped that the design would maximise external validity and statistical power while maintaining an acceptable level of internal validity. The DRCD and SRCD (known collectively as ‘Randomised Consent Designs’\(^{12}\)) randomises patients prior to seeking consent to participate in the trial. The two types of randomised consent design are distinguished according to the extent to which participants are informed about treatment options.

**Double randomised consent design (DRCD)**
The DRCD method randomises patients, tells all patients of their random allocation post randomisation, and then asks for their consent to take part in the study. Patients who refuse the treatment to which they have been randomised can receive the alternative treatment. This means that in a pragmatic RCT of TAU vs TAU + new treatment, patients are told that they

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\(^{12}\) The randomised consent design is also known as the: ‘randomisation prior to consent’ design, ‘post-randomised consent design’, ‘Zelen’s design’ and ‘pre consent design’
have been randomly allocated to TAU & not the new treatment - information which does not happen in routine healthcare. Information as to random allocation to TAU does not replicate the processes of routine healthcare and thus compromises key criteria from the patient’s perspective - key criteria V, VI & VII.

**Single randomised consent design (SRCD)**

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

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

### 5.4.5 Ethical and methodological issues with Randomised Consent Designs

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

Adamson et al. (2005) identified 58 healthcare trials published between 1990 and 2005 using this method, the majority (45/58) of which used the single randomised consent design (SRCD). Most used the randomised consent design to avoid biases associated with patients knowing about alternative treatment (e.g. Hawthorne effects, resentful demoralisation,
avoidance of contamination) rather than as an aid to participant participation (Torgerson & Torgerson, 2008). Most trials experienced some crossover from one group to the other (mean = 13.8%, IQR 2.6% - 15%), although this was usually reported as being ‘within acceptable\(^{13}\) limits’. An ITT analysis was used in 74% of trials. Schellings et al. (2006) identified 50 trials using the randomised consent design with 23/50 trials using the single randomised consent design (SRCD). Of the 29 trials which gave reasons for using the randomised consent design, 16/29 used the method to prevent contamination, and 11/29 used the method to avoid problems with randomisation such as simper IC procedure, simpler participant recruitment, and avoiding unnecessary distress and confusion for patients. Non compliance in those trials that used the SRCD reported a median of 15% (IQR 7% - 39%) in the treatment offer group compared to a median of 0% (IQR 0-4%) in the no treatment offer group\(^{14}\). Reported median loss to follow-up in the SRCD trials was 9% for the treatment offer group and 0% for the no treatment offer group.

5.4.6 Ethical arguments

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

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

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

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

- denial of information to patients regarding all possible trial options prior to randomisation

\(^{13}\) The term ‘acceptable’ here presumably equates to avoiding a Type II error (concluding there is no difference when there is) in the context of an ITT analysis

\(^{14}\) Schellings describes these as the ‘index’ and ‘reference’ groups
- denial of patient choice regarding whether randomised to treatment options
- overselling advocated treatment

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

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

5.4.7 Individual-cluster RCTs

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

5.4.8 Methodological issues of Randomised Consent Designs

The methodological advantages and disadvantages of the design have been discussed widely in the HSR literature (Zelen, 1979; Zelen, 1990; Altman et al., 1995; Schellings et al., 1999; Torgerson & Roland, 1998; Homer, 2002; Dawson, 2004; Boter et al., 2004; Campbell et al., 2005; Schellings et al., 2006). Homer (2002), Dawson (2004) and Boter et al., (2004)

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15 If it is assumed that patients (and parents of patients) participate in research primarily in order to gain direct and/or indirect benefit.
argue for the randomised consent design in situations where requiring prior consent would lead to potentially biased results i.e. to avoid disappointment bias and subjective bias in the recruitment process (Homer, 2002). Torgerson & Torgerson (2008) argue for the design to be used in situations where it is important to estimate the effects on a whole population such as evaluating population based interventions e.g. bone density screening. Schellings et al. (1999) argue that the design may be the best choice for heroin-provision experiment in order to avoid massive drop out or non-compliance in the control group and Schellings et al. (2006) argue for a limited use of Randomised Consent Designs where: (1) Blinding is deemed necessary, but is impossible to achieve by sham procedures (placebo) and (2) The experimental treatment seems attractive to potential participants.

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

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

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

- ‘Cross over’ rates & ITT analysis

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

5.5 Summary

This chapter asked the question: ‘What is an appropriate trial design from the current HSR perspective?’ It described the importance of internal validity in trial design in order to facilitate the drawing of strong causal inferences (Key Criterion VIII: Internal and external validity). In order to identify important issues with regards to both internal and external
validity, a broad and high quality body of literature within HSR – methodology reports of the NHS R&D HTA programme - was reviewed. Critical methodological problems for the external validity of rigorous pragmatic clinical research in the NHS were identified (recruitment numbers, recruitment representativeness, patient and clinician preferences, and informed consent) and a further four key criteria for appropriate trial design were derived from the HSR perspective IX (Recruit sufficient numbers), X (Recruited population is representative), XI (Patient and practitioner preferences unaltered), and XII (Informed consent procedure is not a barrier).

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

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

The next chapter offers an RCT design that attempts to meet all twelve key criteria using elements of two existing RCT designs: the single randomised consent design and the Comprehensive cohort study design
Chapter 6
The ‘Patient Cohort’ RCT design

6.1 Introduction

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

6.1.2 A preliminary answer
Thus, taking account of these key criteria, a preliminary answer to the question addressed by this thesis is: The type of clinical trial design which can provide the information needed to make decisions about the NHS provision of homeopathy is a pragmatic randomised controlled trial, that allows the intervention to function properly for patients (and clinicians), whose results are generalisable to patients ‘with need’, which produces short and long term outcomes for patients, where patients experiences and preferences are the same as in routine healthcare, where information and consent occur as they would do in routine healthcare for patients, where patients in the trial are representative of the ‘with need’
population of patients, yet has both external and internal validity (and thus can establish causality with some degree of certainty).

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

Diagram 6.1 Twelve key criteria for appropriate trial design

6.1.4 Aims & objectives
The aim of this chapter is to fully describe the ‘Patient Cohort’ RCT design. The objectives of this chapter are to:

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

6.2 The ‘Patient Cohort’ RCT design

6.2.1 Defining the ‘Patient Cohort’ RCT design

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

Box 6.1 The ‘Patient Cohort’ RCT design

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

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

6.2.2 Patient centred NHS

The ‘Patient Cohort’ RCT design describes a collection of methods. Throughout the various stages (design, scientific review, NHS ethical review & governance, MHRA approval, the pilot), several different names were used (and considered) to describe this collection of methods. Some examples are ‘Observational sampling Trial’, ‘Split consent RCT’, ‘Randomised Cohort Controlled Trial’, ‘Patient centred RCT’, ‘Modified Zelen trial’, each name emphasising one particular feature or set of features of the design. The cohort is an
essential part of the design and therefore one name that was considered was the ‘Cohort RCT’, however, that did not fully capture the essence of the design. The ‘Patient’ component of the name arose during the writing up period and was incorporated as it reflected the importance of the patient perspective in all stages of trial design and conduct particularly the need for Informed Consent procedures to be relevant to the patient. It seemed important to emphasise that the research design consisted of people who were there by virtue of their primary identity as ‘patients’ rather than research ‘participants’, hence the design became the ‘Patient Cohort’ RCT design.

6.3 An illustration: Obesity research

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

6.3.1 Researching obesity using the ‘Patient Cohort’ RCT design

The Patient Cohort

A sample Cohort\textsuperscript{16} from the ‘with need’ population, the patient group to be investigated is identified e.g. Obese patients with a Body Mass Index (BMI) of $\geq 30$\textsuperscript{17}. Prospective Cohort members are informed that the research is taking place and of the need to obtain information and recruit patients to form an ‘Obesity Cohort’. Two consents are sought: consent to provide data and consent for that data to be used comparatively. Those patients with a BMI $\geq 30$ who consent, then become patients in the Obesity Cohort, and are periodically asked to provide outcomes (e.g. weight, waist measurement, medication, quality of life, comorbidities, visits to GP etc.) at appropriate time intervals (e.g. quarterly). This design is depicted in Diagram 6.2. As observation is inexpensive relative to treatment, and recruitment rates to observational studies are generally high, large numbers of patients can be recruited to the Obesity Cohort.

Identifying patients eligible for Tx A

Sufficient information needs to be collected from the Cohort in order to be able to identify those patients who meet the inclusion/exclusion criteria for any particular trial. When an

\textsuperscript{16} This cohort could be identified either purposively or by consulting existing large routine databases such as the General Practice Research Database (http://www.gprd.com/home/) of anonymised longitudinal medical records from primary care with over 3.4 million active patients from over 450 primary care practices

\textsuperscript{17} The characteristics of the ‘with need’ population define the inclusion criteria for the Cohort
intervention for obesity (e.g. treatment ‘A’) reaches equipoise, all members of the Obesity Cohort who are eligible for Tx A (i.e. meet the inclusion/exclusion criteria for treatment (Tx) A) are identified – these are described as N(A).

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

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

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

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

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

6.4.2 Advantages of the Cohort
The ‘Cohort’ feature provides a number of research benefits: scoping information e.g. the natural history of the disease and any associated factors, information on TAU, long term outcomes, facility for multiple trials, uncontaminated control group, increased comparability of research, strengthened statistical inferences & generalisability.
6.4.3 Scoping information
The Cohort provides scoping\(^{18}\) information that can be used for designing trials. Experimental research needs to be based on up to date observational data as to the normal progression of disease, factors which may influence the course or outcome of the disease, clinicians prescribing patterns, patterns of behaviour by patients, comorbidities etc., however, in many diseases the natural history is not well characterised. Often there is a time lag between changes in the behaviour of populations, and information about these changes being published in the public domain e.g. news of the change in HRT prescribing habits and attitudes to HRT after the publication of the WHI trial data took several years to be published in peer reviewed journals (Ness, 2005). Locating trials within an observational Cohort can provide up to date relevant information and accurate estimates of the public health benefit of any intervention can be gained by gathering data on rates of compliance.

6.4.4 Treatment as usual (TAU)
The Cohort feature embeds the research within existing routine healthcare practice (TAU) and thus allows constant comparison to TAU with any intervention trialled. Indirect comparisons also mean that interventions can be compared with each other as well as TAU. Information from the Cohort can provide the routine, accurate and systematic information that is needed to inform clinical practice and health services management.

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

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

\(^{18}\) The MeSH definition of scoping is: “a means of identifying issues and concerns, their significance and the range of alternatives” (http://cancerweb.ncl.ac.uk/cgi-bin/omd?scoping).
far in the future. The Cohort feature of the ‘Patient Cohort RCT’ thus enables both short and long term outcomes to be produced (Key Criterion II).

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

6.4.7 Increased comparability, statistical power & efficiency
The CASS study (1984) reported in section 5.5.2 demonstrated that recruiting patients to be observed is significantly easier than recruiting patients to be randomly allocated to treatment groups. Because recruitment of patients in standard RCTs is difficult (and expensive) standard RCTs usually randomise patients on a 1:1 basis as this gives the greatest statistical power for the least number of patients. However, for the ‘Patient Cohort’ RCT design, recruitment of patients to the observational Cohort will be easier (and thus cheaper) than recruitment to standard RCTs, thus random selection could be on a unequal basis e.g. 3:1 (i.e. 3 controls: 1 intervention). In order to adequately power any given RCT, it would be possible to have more patients in the control group but less patients in the intervention group than when using 1:1 (equal) randomisation. As well as reducing trial treatment costs, the increased efficiency of the ‘Patient Cohort’ RCT design will result in fewer patients being offered experimental interventions with uncertain outcomes.

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

6.4.9 Attrition
Cohorts are susceptible to attrition (where participants are lost during the study and cannot be included in the analysis) as members of the Cohort recover from their condition (and hence are no longer eligible), move away (mobility attrition), die, or lose interest in the research (compliance attrition, research fatigue attrition). Attrition can reduce the statistical power of the inferences as well as introduce bias when those who drop out of the Cohort
differ from those who continue. The Cohort will need continuous replenishment in order to have sufficient numbers of patients with the condition, and consideration will need to be given to incentives to motivate members of the Cohort to continue providing information. However, attrition in the Cohort should be less than attrition in a standard RCT design where patients are asked to comply with being in a situation with uncertainty regarding treatment allocation, and possible disappointment at not being allocated the preferred treatment as well as being observed\textsuperscript{19}.

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

6.4.11 Cost
The financial cost of the Cohort will depend on the size of the Cohort, the cost of recruiting patients to the Cohort, the cost of obtaining data from the Cohort, the number of elements in the data collection and the attrition rate. The more trials that use any one Cohort then the cheaper each trial will be and the more cost effective it will be to maintain the Cohort. The size of the Cohort needs to be consistent with the plan for its exploitation. Cost should be less than multiple independent ‘SAS’ style trials but may not be so.

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

\textsuperscript{19} Reducing attrition by weaning out non compliers with the intervention or data collection is an issue that has been addressed by the preliminary run in phase of the placebo run-in trial design (section 5.5.8).
6.5 Main features of the design: random selection

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

6.5.2 Definition of random selection
The ‘Patient Cohort RCT’ has operationalised randomisation as random selection of some (n). This contrasts with randomisation in the standard RCT which is operationalised as random allocation of all (N). If randomisation is conceptualised as random selection of some (n) patients from the observational Cohort, then it can be argued that neither information about randomisation, nor consent to be randomised, is relevant to the patient’s status until after they have been randomly selected to a non TAU group. Only those patients who have been selected at random are told post hoc that this is how they have been selected for treatment A. The two methods – random allocation of all (N) and random selection of some (n) are depicted side by side in Diagram 6.3. The ‘Patient Cohort’ RCT design is a form of Single Randomised Consent Design (SRCD) (which has been discussed in chapter 5) where no information regarding randomisation or possible treatments is given prior to randomisation and only those patients allocated to the non TAU group receive information about randomisation post randomisation.

6.5.2 Patient status – in a trial or not?
A lay person’s idea of ‘being in a trial’ is likely to involve trying out a new treatment, not receiving the usual one (Allmark, 1999). But in standard pragmatic trials all patients who are recruited are ‘in the trial’ even if they are randomised to TAU. Patients participating in research that uses the ‘Patient Cohort’ RCT design can be seen to have several different types of status:
1. In an observational Cohort
2. Eligible for an intervention (the ‘with need’ population)
3. Randomly selected to be offered the treatment

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

Diagram 6.3 ‘Random selection of some’ versus ‘Random allocation of all’

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

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

6.6 Main features of the design: ‘Patient centred informed consent’

The third feature of the Patient Cohort RCT is described as ‘Patient centred informed consent’. ‘Patient centred informed consent’ is perhaps better described as a ‘collection of methods’ rather than a single ‘feature’. Chapter 4 described the current standard approach to Informed Consent, with its multiple information and consents all given and sought at a single time point to all patients regardless of what treatment they would ultimately receive (or not receive). Chapters 4 & 5 identified several critical issues associated with the current standard approach to Informed Consent: the patient’s lack of understanding of random/ chance allocation to treatments, the clinician’s and patient’s aversion to uncertainty in the healthcare setting, the fact that Informed Consent often appears to act as a barrier to recruitment. The impact of these critical issues on patient recruitment appeared to suggest that there is a need for a different approach to informed consent. ‘Patient centred informed consent’ offers a different approach and a possible solution to these issues.

6.6.1 Definition

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

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

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

6.6.2 Advantages

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

6.6.3 Patient appropriate information

‘Patient centred informed consent’ enables the information flow to mimic that which exists in routine healthcare – patients are observed and when a treatment becomes available and is deemed that it might be beneficial for the patient then they are given information about the treatment and asked to consider consenting to the treatment. By replicating the processes of routine healthcare uncertainty for the patient is kept to a minimum. ‘Patient centred informed consent’ increases the clarity and certainty for the patient about the research thus enabling the fulfilment of Key Criterion V (Replicate processes of routine healthcare), and Key Criterion VI (patient appropriate information).

6.6.4 Patient appropriate relationships & consent

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

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

Research Ethics Committees will be unfamiliar with the distinction between random selection and random allocation and the need to split the delivery of the different types of information and consent. The current norm for Research Ethics Committees is that all patients involved in research must be given ‘full’ information as to how they have been selected with regards to the research and whatever treatment group they are allocated to. The National Research Ethics Services (NRES) Informed Consent procedure has already been described in Chapter 4.

Diagram 6.5 compares current standard NRES Informed Consent procedures for trials with the ‘Patient centred informed consent’ procedures for the ‘Patient Cohort’ RCT method. We can see that the same information is provided and the same consents are sought in both styles of Informed Consent. There are two fundamental differences however, the first difference is in the timing of the different types of information/consents, and the second difference is that in the ‘Patient Cohort’ RCT treatment information is about treatment that they will receive (if they accept it) rather than about treatment that they might receive (regardless of whether they want it or not).
6.7 Meeting the key criteria
How far does the ‘Patient Cohort’ RCT satisfy the twelve key criteria for appropriate trial design? This thesis argues that the design goes further towards meeting the twelve key criteria than the current standard pragmatic RCT design. Box 6.2 lists the three main features of the ‘Patient Cohort’ RCT design (the Cohort, Random selection of some and ‘Patient centred informed consent’) and its ten additional features.

Box 6.2 Features of the ‘Patient Cohort’ RCT design

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<td>Cohort</td>
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<td>Random Selection</td>
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<td>Patient centred information and consent</td>
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<th>ADDITIONAL FEATURES:</th>
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<td>Uncontaminated control group</td>
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<td>Congruence with motives of patients and practitioners</td>
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The ‘Cohort’ aspect of the ‘Patient Cohort’ RCT design maps onto three key criteria as they enable these three criteria to be fulfilled: Pragmatic RCT (I), Findings generalisable to ‘with need’ population (III) and Produce short and long term outcomes (IV) however the two other main features of the design: ‘Patient centred informed consent’ & ‘random selection’ do not map directly onto any one single criterion, but instead jointly facilitate all twelve key criteria.

Chapter 9 evaluates a pilot of the ‘Patient Cohort’ RCT design as a research tool per se, using information derived from the pilot and attempting to assess the extent to which the pilot of the design met the 12 criteria for appropriate trial design.

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

6.8.1. Ten study designs

Chapter 5 discussed the twelve key criteria in relation to ten RCT designs identified in an HTA report20 (MacLehose et al., 2000). This section now compares the ‘Patient Cohort’ RCT design to these ten RCT designs.

6.8.2. ‘Hybrid designs’

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

Random selection of some vs random allocation of all

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

Consent to randomisation

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

Consent differential

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

Reduced internal validity

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20 This report aimed to investigate the association between methodological quality and the magnitude of estimates of effectiveness derived from RCTs and quasi-experimental and observational studies (QEOs).
The fourth difference between ‘hybrid designs’ and the ‘Patient Cohort’ RCT design is that all patients in the ‘Patient Cohort’ RCT are randomised (randomly selected or not randomly selected) thus maintaining the internal validity of the design whereas ‘hybrid designs’ collect data from both randomised and non randomised patients – thus reducing the internal validity of their designs (Key Criterion VIII).

**Treatment preferences: strong, explicit vs any, non implicit**

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

6.8.3 ‘RCT variants ’

MacLehose et al. (2005) describes six RCT variants: Randomised play– the-winner design, Randomised discontinuation trial, Change to open label, Placebo run-in trial, Single Randomised Consent Design, and the Double Randomised Consent Design. Four of the six RCT variants are designs which address issues unrelated to external validity. The Randomised play– the-winner design aims to minimise the number of patients who receive the less effective treatment – an ethical/efficiency issue rather than external validity issue. The randomised discontinuation trial, Change to open label design and the placebo run-in trial each use placebo in their design and are thus the main difference is that they are designs which address the question of efficacy whereas the ‘Patient Cohort’ RCT design is an ultra pragmatic RCT design which addresses questions of effectiveness.

6.8.4 Randomised Consent Designs

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

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

Non prior consent to randomisation is a central feature of both the Single Randomised Consent Design (SRCD) and the ‘Patient Cohort’ RCT design, however the ‘Patient Cohort’
RCT design offers an evolved version of the SRCD. This evolved version differs from the SRCD in three ways.

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

Secondly, the ‘Patient Cohort’ RCT randomly selects some rather than randomly allocates all as in the SCRD. Those patients in the Cohort are not in a trial until they are randomly selected to be offered the option of trying\(^{21}\) a treatment. Those patients in the Cohort NOT randomly selected are not in a trial but they have given consent for their data to be used comparatively – and this data is used as the comparator data when assessing the effectiveness of the intervention in the RCT.

6.8.6 The ‘Adapted randomised consent (Zelen) design’

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

The ‘Adapted randomised consent (Zelen) design’ was described thus:

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

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

- the initial use of an observational cohort

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\(^{21}\) Both the terms ‘trial’ and ‘try’ have the same root ‘trier’ meaning to sift (Old French)
– staged information & consent (i.e. no information was given to those patients who were not allocated to the intervention and ‘treatment’ information was given after randomisation).

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

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

2. The ‘Patient Cohort’ RCT design operationalises randomisation as ‘random selection of some’ rather than the standard ‘random allocation of all’.

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

### 6.9 Testing the design

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