Is homeopathic treatment more effective than giving time and attention to NHS patients with chronic complaints.

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Submitted in accordance with the requirements for the degree of
Doctor of Philosophy

The University of Leeds
School of Healthcare

September, 2012

The candidate confirms that the work submitted is his/her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

This research has been carried out by a team which has included; Andrea Nelson, Joanne Greenhalgh, Jackie Raw, Clare Walters, Christine Smith, Kate Thomas, Clare Relton, Rachel Roberts, Katy Cooper, Kapil Kapur and Elmuhtady Said.

My own contributions, fully and explicitly indicated in the thesis, have been: the conception and design of the “attention control” arm in the Barnsley Irritable Bowel Syndrome Cohort Study (BIBSC), and the management of the BIBSC and the randomised controlled trial between its commencement in 2010 and December 2011. This phase of the BIBSC and the randomised controlled trial was termed HIBS 1. I took the lead in preparing the HIBS 1 protocol and the research ethics and research and development applications for HIBS 1. I also inputted and analysed all the data for HIBS 1, the results of which are given in this thesis. The other members of the group and their contributions have been as follows: Jackie Raw, Clare Walters, Christine Smith, Kate Thomas and Clare Relton; the conception of a study to explore the effectiveness of homeopathic treatment for irritable bowel syndrome. Clare Relton conceived the idea of using the Cohort Multiple RCT methodology for this study. Kapil Kapur and Elmuhtady Said have provided assistance with the recruitment of participants to the cohort.

The conception, design and analysis of the qualitative interviews was my own. In addition, I conducted all the qualitative interviews with the patients and therapists.

The conception, design and analysis of the Cochrane systematic Review of homeopathy for irritable bowel syndrome was my own. Katy Cooper provided advice on search strategies for the Cochrane review. Rachel Roberts has assisted with the screening and data extraction for the Cochrane review.

My supervisors, Andrea Nelson and Joanne Greenhalgh, have provided advice and guidance throughout.

For the Cochrane protocol, Emily Peckham co-ordinated and led the review. All authors contributed to the drafting of the protocol. Emily Peckham and

Rachel Roberts carried out independent screening of papers and formed consensus on studies for inclusion. Katy Cooper provided advice on search strategies.

The protocol for the randomised controlled trial has been submitted for publication to BMC Complementary and Alternative Medicine. Emily Peckham took the lead role in drafting and revising the manuscript for this publication. Clare Relton, Jackie Raw, Kate Thomas, Christine Smith and Clare Walters all commented on various versions of the draft protocol. All authors read and approved the final manuscript.

Acknowledgements

This thesis owes a great deal to the support and guidance of my supervisors Professor Andrea Nelson and Dr. Joanne Greenhalgh. Special thanks also to Professor Kate Thomas and Dr. Clare Relton for their initial supervision in the first year.

I would like to take this opportunity to express particular gratitude to the team at Barnsley Hospital, Dr Kapil Kapur, Dr. Elmuhtady Said, Dr. Christine Smith, Dr. Clare Walters and Mrs Jackie Raw. I have enjoyed being part of the team.

Thanks also to Theresa Munyombwe who kindly provided statistical advice and guidance.

None of the work in this thesis would have been possible without the financial support from a studentship from the School of Healthcare at the University of Leeds. My thanks go to them for their support.

I also owe a great deal of thanks to the patients who participated in the study reported in this thesis. Their interest and time has been very much appreciated.

Thank you to my husband, children and parents for all your love, support and encouragement.

Finally thanks also to my fellow PhD students whose support, advice and kindness has helped me through my studies.

Abstract

Many people seek individualised homeopathic treatment, however its use remains controversial. There have been suggestions that any improvement of the symptoms of those seeking individualised homeopathic treatment is solely down to the time and attention given to the patient by the homeopath.

This aim of this thesis is to explore the question “is homeopathic treatment involving a homeopathic consultation and a homeopathic remedy any different to spending time with an empathetic practitioner, in the treatment of irritable bowel syndrome?”

This study involved a systematic review of homeopathic treatment for irritable bowel syndrome and a randomised controlled trial comparing individualised homeopathic treatment to supportive listening and usual care. The primary outcome measure was the change in irritable bowel symptom severity score at 26 weeks. Differences between the three arms were assessed using independent t-tests and ANCOVA.

A qualitative study nested within the randomised controlled trial involved qualitative interviews with a proportion of the participants in both the homeopathic treatment and supportive listening arms. This was to explore participants’ experiences of the treatment they received, and what, if anything about the treatment they felt led to any improvements.

The systematic review of homeopathic treatment for irritable bowel syndrome identified two eligible RCTs, a meta-analysis of the results of these trials indicated a benefit of homeopathic treatment over placebo. However the results of this review should be viewed with caution as it is possible that there was a degree of bias associated with these two trials.

In the randomised controlled trial, no significant differences were found between homeopathic treatment and supportive listening, when using t-tests or ANCOVA to compare mean change in IBS-SSS between baseline and 26 weeks.

The qualitative interviews identified four different typologies that explained what patients believed to have led to changes in their general health and/or irritable bowel symptoms.

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List of Abbreviations

AC:	Attention control
BIBSC:	Barnsley irritable bowel syndrome cohort study
CARE:	Consultation and relational empathy
EQ-5D:	Euro-Qol-5D
HADS:	Hospital anxiety and depression scale
IBS:	Irritable bowel syndrome
IBS-SSS:	Irritable bowel syndrome symptom severity scale
IBS-Qol:	Irritable bowel syndrome quality of life measure
IHT:	Individualised homeopathic treatment
mcRCT:	Multiple cohort randomised controlled trial
PCT:	Primary care trust
RCT:	Randomised controlled trial
SoH:	Society of Homeopaths

1 Introduction

This thesis reports a study of the effectiveness of homeopathy in the treatment of irritable bowel syndrome (IBS). The aim of this thesis is to evaluate whether or not homeopathic treatment involving a homeopathic consultation and a homeopathic remedy (hereafter referred to as individualised homeopathic treatment or IHT), is effective in the treatment of IBS.

The idea for this thesis began in 2005 following the publication of a meta-analysis of trials of homeopathy that concluded that homeopathy was no better than placebo (Shang *et al.* 2005). This publication led the author to consider previous trials of homeopathy and their strengths and weaknesses. The author has worked as both a professional homeopath, and as a chemist in commercial research. This combined experience led her to question whether or not it was possible to carry out a study into the effectiveness of IHT that was acceptable to both homeopaths and the scientific community. The validity of studies designed to test the effectiveness of IHT have in the past been criticised by homeopaths for not being a true reflection of how IHT is delivered in practice, and by the scientific community for methodological weaknesses, in particular being biased towards IHT. The author therefore wanted to explore whether it was possible to design a trial of IHT that was true to how homeopathic treatment is delivered in practice, without the methodological weaknesses that have in the past been associated with trials of homeopathy.

One of the criticisms of homeopathy is that it is the time and attention given to the patient by the homeopath that leads to any improvement in patient outcomes (McKie 2005). Considering this criticism led to the question “is homeopathic treatment involving a homeopathic consultation and a homeopathic remedy any different to spending time with an empathetic practitioner?” In an attempt to answer this question this thesis has three components, a systematic review into the effectiveness of IHT for IBS, a randomised controlled trial (RCT) of IHT and nested within the RCT, a qualitative study exploring RCT participants’ beliefs about the treatment they received. A qualitative element was included in the study because, whilst the RCT would be able to give information about the effectiveness of IHT, it would not be able to give information about what it was about IHT that led to any improvements in IBS and/or general health. This thesis therefore

describes the three components of the study, with this chapter providing an overview of the thesis and its structure.

Chapter 2 lays out the conceptual issues and details the complexity that had to be tackled before proceeding. It also provides an explanation of what homeopathy is and the different types of homeopathic treatment. Chapter 3 describes the systematic review of homeopathy for IBS, giving information on the methods used, search strategies and results found. Using the MRC framework for complex interventions, IHT can be thought of as a complex intervention (Medical Research Council 2000). Complex interventions are interventions comprising of a number of elements, which may operate both independently and inter-dependently. These elements appear to be essential to the functioning of the intervention, however it is difficult to precisely identify the active ingredient of the intervention (Medical Research Council 2000). IHT can be thought of as complex intervention with two components; the homeopathic consultation and the homeopathic remedy, in addition to which, is the possibility of an interaction between these two components. This means that, as with all complex interventions, there are inherent challenges in designing trials of IHT. These challenges are discussed in Chapter 4 along with the types of trials that have so far been used to explore the effectiveness of IHT and other forms of homeopathy. In light of these difficulties Chapter 5 considers to how to construct an attention control for IHT as an alternative to the traditional placebo-controlled trial, defining a potential attention control for IHT, namely supportive listening. Chapter 6 explains the methodology for both the RCT and the qualitative study and Chapter 7 describes the methods used in these studies. Due to the belief held by some, that homeopathy is nothing more than a placebo and it is unethical to carry out trials of placebo treatments (Smith 2012), there are ethical concerns associated with carrying out a trial of homeopathy. Therefore Chapter 8 focuses on this and other ethical concerns associated with both the RCT and qualitative study. Also contained within this chapter is a discussion on the potential for author bias and how this was dealt with. Details of the results of the RCT are given in Chapter 9, whilst results from the qualitative study are given in Chapter 10. Finally Chapter 11 gives a discussion of the results of each of the components of the thesis before discussing what the combined results say about the effectiveness of homeopathic treatment for IBS. Chapter 10 also discusses strengths and limitations and some of the challenges involved in conducting this study. Implications for practice and policy, along with recommendations for future study are made in Chapter 11.

This thesis contributes to the literature on the design of trials for assessing the effectiveness of IHT. It provides information on the feasibility of carrying out a trial comparing the effectiveness of IHT to an attention control for patients with IBS, which may be used to inform the design of future trials. In addition it contributes to the literature base on the effectiveness of homeopathy for IBS. The qualitative study contributes to the knowledge regarding patients perceptions of what, if anything about IHT that leads to any improvements in IBS symptoms and general health.

2 Homeopathy and placebo

This chapter sets out to describe the contextual issues that underpin this thesis. Knowledge of these contextual issues is necessary to understand not only why the evaluation of homeopathy is important but also why the evaluation of homeopathy is not straightforward. The chapter opens with a brief explanation of complementary and alternative medicine (CAM) before moving on to discuss homeopathy, in terms of the history of homeopathy and the different types of homeopathy available. Although homeopathy is available on the NHS, its inclusion is contentious (House of Commons Science and Technology Commitee 2010). Therefore, the reasons why homeopathy is so contentious, and the relevance of evidence based medicine to the debate about whether or not to include homeopathy on the NHS is explored. Much of the controversy surrounding homeopathy is due to the view that it is a placebo treatment (Ernst 2010), consequently the chapter concludes with an exploration of the nature of placebos and different understandings of what a placebo is.

2.1 Complementary and alternative medicine

CAM is a broad and constantly changing discipline, which makes it difficult to define. The website for the United States National Center for Complementary and Alternative Medicine (NCCAM) defines CAM as “a group of diverse medical and healthcare systems, practices and products that are not generally considered part of conventional medicine.” (National Center for Complementary and Alternative Medicine 2012). This quote reflects the diversity of treatments that could be considered to be CAM. The fact that the quote mentions that CAM treatments are not “generally” considered part of conventional medicine highlights the fact that there is no consensus as to whether some treatments should be considered to be part of CAM, or whether they should be considered to be part of conventional medicine. It is this uncertainty that leads to the difficulty in providing an absolute definition for what is, and what isn’t, a CAM treatment.

CAM has been a growing field in the UK (House of Lords 2000; Ernst 2008) since the 1980’s.There was little research into its exact usage until the end of the 20th century when studies showed that 15-20% of UK citizens used CAM in some form each year (Thomas, Nicholl and Coleman 2001; Thomas, Coleman and Nicholl 2003). A questionnaire-based survey found that this

was due to patients' dissatisfaction with the results of conventional medicine (Astin 1998). Furthermore interviews with CAM users found that conventional medicine was viewed as lacking in holism, where the body is treated as separate parts rather than being viewed as a whole system (Barrett *et al.* 2003). CAM is viewed by some as being more individual than conventional medicine, prioritising the doctor-patient relationship and promoting wellbeing rather than healing illness (Veeramah and Holmes 2000; Bishop, Yardley and Lewith 2006), along with seeing the body as a whole system (Barrett *et al.* 2003). The majority of CAM treatments seek to treat the whole person rather than the diseased part and involve a much longer consultation time than that provided in the NHS. The bulk of CAM consultations are paid for out of pocket (Thomas, Nicholl and Coleman 2001), which gives an indication of the values that people place on CAM. This thesis is concerned with homeopathy, a form of CAM. To put homeopathic treatment into context the basic principles of homeopathy are explained below.

2.2 Homeopathy

Homeopathy (also spelt homoeopathy) can be thought of as a system of medicine based on treating the individual, by giving medicines known as remedies, prepared from substances that have been highly diluted and succussed (shaken). It was first developed by Samuel Hahnemann in the 18th century in Germany and works on the principle of "like cures like" - that is, a substance that would cause symptoms in a healthy person cures those same symptoms in illness. For example, one remedy which might be used in a person suffering from insomnia is coffea, a remedy made from coffee.

Hahnemann originally trained as a medical doctor but became disillusioned by the brutal medical practices at the time and because of this started working as a translator (Blackie 1990). Dissatisfied with the explanation that the reason cinchona relieved malaria symptoms was because it was bitter, he decided to take some himself. He found that he then developed some of the symptoms of malaria and came up with the theory that "like cures like", i.e. something that causes symptoms in a well person will cure those same symptoms in a sick person (Vithoulkas 1998). Following on from this he began to test more substances, some of which were poisons, leading to his decision to dilute and succuss them prior to taking them (Blackie 1990). He claimed that, from his observations, the more dilute a substance was, the more powerful its effects as long as it was succussed (Hahnemann 1996). It

is these high dilutions, many of which are beyond Avogadro's number which is 6×10^{-23} (meaning none of the original substance is left), that have led to scepticism about homeopathy and questions over how something diluted beyond Avogadro could exert any physical effect. Many detractors of homeopathy see it as implausible and there has been a number of calls for the end of homeopathy, such as the editorial in the Lancet in 2005 entitled "The End of Homeopathy" (Anonymous 2005a). Yet homeopathy is more than just the remedy, the consultation and the tailoring of the remedy to the individual person were key aspects of Hahnemann's Organon, (the book written by Hahnemann explaining homeopathy and its philosophy). Therefore criticising homeopathy on the grounds of the implausibility of the remedy fails to take into account whether or not there is any effectiveness specific to the homeopathic consultation and remedy matching process.

Despite the controversy surrounding homeopathy, it is a popular complementary medicine which has been available on the NHS since its inception in 1948. Not only is it integrated into the NHS in parts of the UK, it is also integrated into the health systems of other countries such as Pakistan, India, Sri Lanka and Mexico (World Health Organization 2002). It is one of the five most used CAM based therapeutic systems in the world (World Health Organisation 2001) and is popular in the UK, continental Europe, Asia and North America. A UK survey has shown that 1.2% of the population had consulted a homeopath in the 12 months prior to the survey and 8.6% had bought an over-the-counter homeopathic remedy (Thomas, Nicholl and Coleman 2001). It is possible that there may be a response bias to this survey, as the data was collected via a postal questionnaire, which would require that respondents be English speaking and literate. Furthermore those people who had used homoeopathy may be more likely to respond to a survey about CAM than people who had no interest in CAM. Therefore these results should be thought of as relating to the adult, literate English speaking population. Despite this a further survey, where supplementary questions about CAM usage were added to a National Omnibus Survey, found that 1.9% of the population had visited a homeopath in the past 12 months. The National Omnibus survey is carried out by the UK Office for National Statistics on behalf of the government, public and not for profit bodies, and aims to give a nationally representative estimate about individuals and households. Therefore whilst the possibility of a response or sampling bias cannot be ruled out, an Omnibus sample has been found to be comparable to Census data (Thomas and Coleman 2004).

2.2.1 Types of homeopathy and homeopaths

The issue of whether “homeopathy” is more than placebo is compounded by the fact that the term “homeopathy” is used to describe several different styles of homeopathic treatment, classical, clinical and complex (Relton, O'Cathain and Thomas 2008). Classical also called individualised homeopathic treatment (IHT) (Katz *et al.* 2005) is the form most commonly practised in the UK.

IHT involves a detailed case taking where the homeopath seeks to understand the patient’s symptoms and their experience of their symptoms, and from this prescribes a remedy individualised to that patient. The ideal of IHT is to identify one remedy that fits the totality of the patient’s symptoms and thus aims to address all that person’s problems. In contrast to this, in continental Europe, practitioners practice clinical homeopathy (sometimes known as therapeutic homeopathy or therapeutic prescribing), where prescriptions involve the use of specific remedies for individual diseases. It is of note that clinical homeopathy’s model of homeopathic prescribing is more aligned with the biomedical model of health and disease than the model used in IHT. For example if a person with irritable bowel syndrome and migraines were to go to a homeopath who used clinical homeopathy, they would usually receive two remedies, one thought to have an affinity with the gastrointestinal tract, and another thought to be one of the “headache” remedies. The consultation time would be relatively short because clinical prescribing does not require a complete picture of the patient to make a prescription, rather it merely requires the symptoms of the irritable bowel syndrome and those of the migraines. However if the same person went to a homeopath who prescribed according to the principles of IHT, the homeopath would ask questions not only about the irritable bowel syndrome and the migraines, but also about any other problems the person may be having, along with more general questions about the type of person they are, their likes and dislikes etc. The homeopath would then try to find one remedy that covers all the patient’s symptoms and also fits their general state. This one remedy would aim to address all the patient’s problems rather than breaking them up and prescribing for each problem, as is the way in conventional medicine. Thus homeopaths using the IHT model are less concerned with biomedical diagnoses and more concerned with the person’s symptoms picture. Looking to treat the whole person and not a disease label.

The final type of homeopathy is complex homeopathy, so called because it involves the use of homeopathic “complexes”, which are a combination of remedies and sometimes herbal medicines as well. These complexes are often available over the counter such as Pollena™, a homeopathic complex sold in the UK for hay fever. Complex homeopathy tends to be practised by practitioners trained in a variety of CAM therapies, rather than by homeopaths, and does not require a detailed description of symptoms.

Another form of treatment known as isopathy is sometimes confused with homeopathy. This confusion arises because the substances prescribed in isopathy are diluted in the same way as homeopathic remedies. However, isopathy is not concerned with enquiring about symptoms but merely involves the prescribing of the thing thought to have caused the problem in the first place i.e. in poison ivy rash isopathy would advocate prescribing rhus tox a homeopathic medicine made from poison ivy (Coulter and Dean 2007), whereas in IHT a homeopathic medicine would be prescribed based on the persons symptoms.

In the UK there are two types of qualified homeopaths, professional homeopaths who have completed a three to four year course in homeopathy but are not trained doctors, and medical homeopaths who are trained doctors, vets or dentists with additional training in homeopathy. As it is the most common form of homeopathic treatment for chronic complaints, this thesis focuses on IHT (McCarney, Linde and Lasserson 2004).

To provide a context for the debate surrounding the inclusion of homeopathy in the NHS, the next section will discuss evidence based medicine, the National Institute for Health and Clinical Excellence and how they relate to the inclusion of homeopathy within the NHS.

2.3 Evidence based medicine

The National Institute for Health and Clinical Excellence (NICE) is the independent organisation responsible for providing guidance on the prevention and treatment of ill health and the promotion of good health. NICE guidance aims to ensure that people living in England and Wales have the same access to medicines that are considered to be clinically effective and cost effective, and to reduce uncertainty about which treatments should be used (National Institute for Health and Clinical Excellence 2012). It should be noted that there is a difference between efficacy and effectiveness, with efficacy being whether the drug or procedure generates the required clinical

outcome under ideal conditions and effectiveness being; does the drug or procedure work under usual circumstances (Compher 2010).

Evidence based medicine (EBM) arose as a consequence of variations in medical practice, with some treatments being used that had no evidence of effectiveness. The practice of EBM therefore requires the “conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients” (Sackett *et al.* 1996) page 71. However this definition fails to take into account patient choice, therefore Evidence Based Nursing Practice suggests a definition by Muir Gray, which seems more helpful, "an approach to decision making in which the clinician uses the best evidence available, in consultation with the patient, to decide upon the option which suits the patient best" (Evidence Based Nursing Practice 2003). When thinking about individual patients, EBM means integrating the best available evidence with clinical expertise and patient choice. This means that, for the practice of EBM, research to judge the efficacy of treatments is needed, with the strongest evidence for effectiveness being the randomised controlled trial (RCT) or preferably systematic reviews of a number of high quality RCTs (Lohr, Eleazer and Mauskopf 1998). The rise in EBM has led to the demand that CAM therapies be subjected to the same rigorous assessment as conventional medicine, particularly with the use of RCTs to assess CAM (Miller *et al.* 2004). If a treatment is recommended by NICE the NHS is expected to fund that treatment, hence the need for evidence of the effectiveness of CAM therapies for them to be provided by the NHS. Where a CAM treatment is not available on the NHS, people who want it have to pay for it out of their own pocket, thus limiting patient choice to only those who can afford to pay. At the same time, it would be clearly undesirable for ineffective treatments to be paid for by the NHS. This means that there is a need for treatments to be evaluated, so that those treatments found to be beneficial, can be made available to all who desire, and would potentially benefit from, that treatment.

2.4 Homeopathy and the NHS

Historically homeopathy has been available on the NHS since the NHS was founded, and it has been up to individual doctors and PCTs to decide as to whether or not their patients can access it on the NHS. Although there are currently no NICE guidelines for homeopathic treatment, at present approximately 30 per cent of NHS primary care Trusts (PCTs) continue to fund homeopathic treatment (Moberly 2011). There are also three

homeopathic hospitals (Bristol, Glasgow and London), which provide outpatient treatment. However homeopathy's availability on the NHS remains contentious: a recent report from the House of Commons Science and Technology committee stated that "the government should stop allowing the funding of homeopathy on the NHS" (House of Commons Science and Technology Committee 2010) page 45 paragraph 110. Much of the criticism levelled at homeopathy is that the remedy is no more than a placebo and it is the long consultation time with an empathetic practitioner that leads to any perceived effectiveness of homeopathic treatment (McKie 2005). This led the House of Commons report to conclude, "Placebos should not routinely be prescribed on the NHS. The funding of homeopathic hospitals – hospitals that specialise in the administration of placebos – should not continue" (House of Commons Science and Technology Committee 2010) page 45 paragraph 111. The government's response to this was thus, "our continued position on the use of homeopathy within the NHS is that the local NHS and clinicians, rather than Whitehall, are best placed to make decisions on what treatment is appropriate for their patients – including complementary and alternative treatments such as homeopathy - and provide accordingly for those treatments" (Cabinet Office 2010) page 4 paragraph 8. This statement appears to be in some conflict with EBM which relies heavily on evidence rather than clinical judgement. However the government may have political reasons for not wanting to completely remove homeopathic treatment from the NHS, such as not wanting to be seen to be limiting patient choice. Furthermore, although EBM requires that one seeks out evidence, the practice of EBM does not suggest that clinical judgement should be disregarded altogether, rather the four elements of: evidence, resource constraints, patient's choice and clinical judgement should be used in decision making.

Despite the government's response to the Science and Technology Committee, there remains a strong lobby against CAM, and homeopathy in particular, as evidenced by Simon Singh's recent campaign against Radio Surrey's inclusion of a feature on homeopathy (Singh 2012). The focus of the anti-CAM lobby's argument is that there is no evidence to prove CAM's efficacy, and in the case of homeopathy, the implausibility of how the homeopathic remedy could act given current scientific understanding. The anti-homeopathy lobby and the movement against the inclusion of homeopathy on the NHS, has resulted in a number of PCTs discontinuing funding for homeopathy and the closure of the Tunbridge Wells Homeopathic Hospital. The reason for discontinuing funding for homeopathy

has been cited as being due to the lack of evidence as to its efficacy (NHS Wirral 2011). This reasoning is flawed, and does not explain the whole picture, as 46% of commonly used treatments have unknown effectiveness (Garrow 2007). However the lack of evidence of efficacy could be being used as a convenient excuse by some, to hide more political and economic reasons for not wishing to include CAM in the NHS.

Whatever the reasoning, the refusal of some PCTs to fund homeopathy has had an impact on patients' choice. It is therefore important to understand whether or not homeopathy works in terms of its continuing provision on the NHS. However how best to determine this has been the topic of much debate (Bell 2005). In addition it is also important to know whether or not homeopathy is a safe treatment. In light of this the next section discusses the ethical implications of homeopathy and trials of homeopathy.

2.4.1 Ethics of trials of homeopathy

In addition to the debate about whether homeopathy should remain available on the NHS, there have been questions raised over whether or not homeopathic treatment is ethical. In one of the most recent articles on the ethics of homeopathy Smith (Smith 2012) goes as far as to suggest that the implausibility of homeopathy makes it ethically unacceptable and that it is the moral duty of citizens to reject it. Furthermore there have been suggestions that trials of homeopathic treatment are unethical *"There has been enough testing of homeopathy and plenty of evidence showing that it is not efficacious…"* (House of Commons Science and Technology Committee 2010) page 21 paragraph 77. "*It is also unethical to enter patients into trials to answer questions that have been settled already*" (House of Commons Science and Technology Commitee 2010) page 21 paragraph 78. However, stating that homeopathy as a whole is not efficacious is disingenuous, as there have been RCT trials and systematic reviews that have shown homeopathy to have been efficacious in certain conditions, such as childhood diarrhoea (Jacobs *et al.* 2003) and rheumatic disease (Jonas, Linde and Ramirez 2000). Writing these studies off without proper critique is not beneficial to people with these conditions who could potentially benefit from homeopathic treatment. In addition, given these results, it would be useful to understand further what it is about homeopathic treatment that leads to these apparent benefits. Whilst it is possible that the results of these trials are anomalies, and differences found where none really existed, this can be true of any studies where the results have not been replicated. Therefore until there is a definitive answer as to whether or not homeopathic

treatment works, there is justification in continuing to explore whether or not homeopathic treatment is beneficial. Furthermore research carried out into “ultra high dilutions” of substances diluted beyond Avogadro’s number has found some evidence of differences between ultra high dilutions made using a substance and distilled water and distilled water alone. This research is briefly discussed in section 2.5. Despite this, in a discussion of homeopathy from a utilitarian perspective, Smith (Smith 2012) goes even further by suggesting that because homeopathy is implausible then any positive results would necessarily be false positive results and these results, if reported, could lead to misinterpretation and unjustifiable credibility being given to homeopathy.

The questions over the ethics of homeopathy have been compounded by an influential meta-analysis conducted by Shang (Shang *et al.* 2005). This meta-analysis was accompanied by an editorial in the Lancet questioning whether this was the end of homeopathy (Anonymous 2005a) because it had been unable to conclude that homeopathy was more effective than placebo. However, of the five systematic reviews that reviewed all RCTs for homeopathic treatment regardless of condition, four have concluded that homeopathic treatment is different to placebo (Kleijnen, Knipschild and Terriet 1991; Boissel *et al.* 1996; Linde *et al.* 1997; Cucherat *et al.* 2000). These systematic reviews did not specify a condition which they were studying, rather they identified all RCTs of homeopathic treatment for all conditions (that a RCT had been carried out for) and then carried out their review. It is questionable as to the relevance of these systematic reviews as they have tried to review homeopathy for all conditions and it may be that whilst homeopathy is effective for one condition it is ineffective for another, thus combining all conditions together could lead to erroneous or confusing results. In addition it is likely that there would be a high degree of heterogeneity between the trials, again leading to the possibility of erroneous conclusions. In fact some of the criticism of the Shang study (Shang *et al.* 2005) lies in the high degree of heterogeneity between their included studies and the fact that their conclusions on the effectiveness of homeopathy depend on the set of analysed trials (Ludtke, Rutten and Rutten 2008). Hence, if they had chosen to analyse, from the trials they identified, a different set of trials than they chose, the results would be different. This is primarily due to the inclusion of one negative trial on preventing muscle soreness in long distance runners (Tveiten *et al.* 1998). Due to the high heterogeneity between the studies included in the meta-analyses carried out

as part of these five systematic reviews of homeopathy, it is difficult to ascribe any meaning to the results of these meta-analyses.

Regardless of this controversy, the frequency with which people consult homeopaths may be some indication of the value which they place on the homeopathic approach (Spence and Thompson 2005) and hence the need to identify if it is effective, in order to inform patients.

The view that homeopathy is a placebo, and therefore should not be used, feeds into a wider debate on the use of placebos and indeed the debate about what constitutes a placebo. This debate is reviewed in the following sections, however an overview of the research into ultra high dilutions is discussed first, some of which has found intriguing results.

2.5 Ultra high dilutions

This section provides a brief overview of some of the research that has been carried out into Ultra high dilutions (UHD's). Whilst the area of study in this PhD is not about the basic science of UHDs, a brief summary is given here to give an outline of what UHD research might tell us about the nature of ultra-highly diluted solutions, such as those that form the basis of homeopathic remedies.

Research into ultra-high dilution (also known as serial dilution and agitation), is concerned with the basic science behind homeopathy and the properties of UHDs. A systematic review published in 2007 (Witt *et al.* 2007) assessed the evidence base for laboratory studies of UHDs. These were not studies carried out on people or animals but studies exploring the physical properties of UHDs. Of 67 published studies that were evaluated, 75% found ultrahigh dilutions to have an effect, where an effect was taken to be any observed difference between the UHD and water, as measured by nuclear magnetic resonance (NMR), calorimetry and thermoluminecence. However it should be noted that there were large number of different experimental approaches used and that in a subject as controversial as homeopathy a publication bias is not unlikely. It is possible that studies that did not show any difference between UHD's and water have not been published, and were therefore not included in Witt's review i.e. there may be an element of publication bias at play.

Studies carried out by independent laboratories measuring the physical properties of ultra-highly diluted solutions using techniques such as calorimetry, spectroscopy and thermoluminecence have been conducted

(Rey 2003; Elia *et al.* 2004; Roy *et al.* 2005; Rao *et al.* 2007). Such studies have found differences between homeopathically prepared solutions and control samples (such as water or other solvents). Whilst not giving information as to how homeopathic medicines may work, these experiments demonstrate that it is *possible* that ultra-high dilutions have specific physical properties, despite not containing any of the original molecules. The knowledge that UHDs may have specific physical properties and future exploration of these properties may lead to a greater understanding of how homeopathy may or may not work.

The focus of this chapter will now move on to placebos and the placebo effect, beginning with a discussion on the nature of placebo.

2.6 The nature of placebo

The Oxford English Dictionary online gives the following definition of placebo:

“a medicine or procedure prescribed for the psychological benefit to the patient rather than for any physiological effect.

- a substance that has no therapeutic effect, used as a control in testing new drugs.
- a measure designed merely to humour or placate someone: *pacified by the placebos of the previous year, they claimed a moral victory*

Origin: late 18th century: from Latin, literally 'I shall be acceptable or pleasing', from placere 'to please'” (Oxford Dictionaries 2011), online source.

This definition sets the scene for the idea that placebos inherently involve the deception of patients. Through giving the patient a substance or treatment that the patient believes will help them, it actually will help them, despite the fact that there is no evidence that the substance or treatment in question has any biological effect. This definition is not comprehensive in that it fails to take account of the fact that placebos can be effective in terms of reduction of symptoms and can lead to a therapeutic effect, which will be discussed later on in this section. Firstly, however, it is useful to provide a brief overview of the history of placebo to set the scene for current thinking.

Prior to world war II, when paternalistic attitudes to the ethics of medicine prevailed, (i.e. before the era of informed consent where patients are now given all the facts and no attempts are made to deceive patients), placebos were routinely given as a means of granting patients peace of mind

(Kaptchuk 1998). Placebo was given to people as a kind of benign deception, in the thought that it would not harm the patients and the action of giving something to take may make them feel better. Thus they were given to humour patients rather than because they were thought to be effective. However things began to change during the 1950's and placebos became commonly acknowledged as powerful following an estimate by Beecher that treatment with a placebo leads to an improvement in symptoms in approximately one third of cases (Beecher 1955). Beecher based this estimate on an analysis of 15 studies that had used a placebo, calculating the average percentage of patients who were satisfactorily relieved by a placebo across the 15 studies. The 15 studies comprised nine different conditions. However in his study Beecher didn't take into account regression to the mean, natural history of the condition or concurrent interventions, which also have the potential of leading to an improvement. Therefore despite its wide acceptance, the figure of around 30% response to placebo may be misleading. Regression to the mean is the term used to describe the phenomenon that occurs when variables "regress to the mean". If on first measurement a variable is found to be at either of the extreme ends of a scale, then it is likely that on a second measurement it will have moved closer to the average score i.e. those at the extreme ends of the scale will regress towards the mean (Torgerson and Torgerson 2008). Despite the problems with Beecher's study the results remained unquestioned, with few medical researchers interested in quantifying the placebo effect, either in terms of investigating possible mechanisms of action or confirming Beecher's results (Wampold *et al.* 2005). In addition to this, although Beecher surmised that the mechanism by which the placebo effect occurs deserved more study, until recently there had been little, if any interest in exploring this mechanism or mechanisms.

It wasn't until a publication in 2001 by Hróbjarsson and Gøtzche (Hrobjartsson and Gotzsche 2001) that people began to question Beecher's results. Hróbjarsson and Gøtzche claimed that there was little evidence to suggest that placebos had powerful clinical effects except possibly in treatments for pain (Hrobjartsson and Gotzsche 2001). Hróbjarsson and Gøtzche based this claim on a meta-analysis that they carried out to estimate the placebo effect. Hróbjarsson and Gøtzche identified trials published before 1999 that compared active treatment, placebo treatment and no treatment and compared the results of the placebo arm to the no treatment arm. Inclusion was not limited by condition; therefore a wide variety of conditions was included in this study. An update to this study was

published in 2004 with similar findings (Hrobjartsson and Gotzsche 2004). Hróbjarsson and Gøtzche 2004 concluded that they were unable to find evidence for a large effect for placebos in general. However there was the possibility of a small effect in pain studies that used a patient measured continuous outcome, but this could not be clearly distinguished from bias. The overall conclusion from both Hróbjarsson and Gøtzche's studies, that there was little evidence to suggest that placebos had powerful clinical effects, fails to take into account of the fact that different disorders may have lesser or greater placebo effects (Wampold *et al.* 2005).

Although overall estimates of the placebo effect may indicate that the placebo effect is not large, it could be that there is a large placebo effect for some conditions/situations and a smaller effect for others. Furthermore, Hróbjarsson and Gøtzche's studies (Hrobjartsson and Gotzsche 2001; Hrobjartsson and Gotzsche 2004) failed to take into account the fact that the patients' expectations regarding the efficacy of the treatment may differ for different treatments and/or different conditions. Patients' expectations are important because they are part and parcel of the "placebo effect," and it is through these expectations that placebos "work." It is likely that factors such as how impressive the treatment is, how invasive it is, its plausibility, its cost and its perceived mechanism of action, will all play a part in patient's expectations (Ernst and Resch 1995). Therefore it is possible that Hróbjarsson and Gøtzche's 2001 and Hróbjarsson and Gøtzche's 2004 studies did not lead to an accurate estimate. Indeed in Hróbjarsson and Gøtzche 2001 it was admitted that there was significant heterogeneity in the outcomes produced by placebo in the studies they identified. This heterogeneity could be the result of variables other than the placebo effect, such as regression to the mean, which may not have been consistent across all studies. Alternatively it could be that there are different mechanisms for different conditions/settings i.e. the placebo effect is not heterogeneous in size or mechanism. However if the placebo effect genuinely varies across different conditions, then placebo must exist in some form or another. If it didn't exist it would be impossible for one placebo to be more effective than another placebo (Kirsch 2005), and therefore placebo must exert some form of an effect. Whether or not this effect results from a single mechanism of action or whether different mechanisms of action occur in different situations is important. However of more importance is the fact that the placebo effect can vary because this signifies that it must exist. The studies used in Hróbjarsson and Gøtzche's 2001 study have been reanalysed by Wampold (Wampold *et al.* 2005). In his reanalysis Wampold categorised each study as

to whether the design of the study was adequate to estimate the placebo effect and the degree to which it was expected that a placebo would help the disorder being studied. A study was considered to be adequate to estimate the placebo effect if it was; double blind, the participants were aware that they may receive a placebo and the placebo was not administered surreptitiously, and the treatment and the placebo were indistinguishable. The decision regarding the degree by which a placebo was expected to help was made through deciding whether the condition was amenable to psychological factors, with the theory that conditions amenable to psychological factor would be amenable to placebo. Wampold found that when the results from Hróbjarsson and Gøtzche's 2001 meta-analysis were disaggregated on the two categories described above, evidence for a placebo effect was found. In fact a relatively large effect was observed in adequately performed studies where the condition was amenable to placebo effects and a continuous outcome was used (Wampold *et al.* 2005). However if the placebo effect varies according to condition, patients expectations, mode of delivery etc, then it is not something that is readily quantifiable (in terms of a single number that is true across all conditions and situations). In fact the placebo effect may not result from one single mechanism of action, therefore trying to tie it down to a specific figure is not particularly useful in furthering the understanding of how and why the placebo effect works. *"Indeed, the construct itself remains an enigma to this day",* (Borkovec and Sibrava 2005) page 806. More useful perhaps would be an understanding of the mechanism through which an inactive drug may lead to an improvement.

To add further uncertainty as to what exactly is the "placebo effect" and its definition, it has been found that, between 1981 and 2000 the percentage of people suffering from depression who have responded to placebo medication (and genuine anti-depression medication) has increased by around 7% per decade (Walsh *et al.* 2002; Khan *et al.* 2005). Responding to placebo was defined as a reduction of at least 50% on the Hamilton Rating Scale for Depression (Williams 1988) and/or a Clinical Global Impression (Guy 1976) rating of markedly or moderately improved. This figure may be skewed by the fact that only published studies were included in the analysis, however it is thought unlikely that unpublished studies would have found a higher figure for the placebo effect than found in published studies. Therefore it possible that the figure may be higher than the 7% quoted. This increase leads to the notion that some factor of placebo response must have changed over the years. It is possible that clinically important characteristics

of patients involved in treatment studies and/or the definition of “depression” has changed over the years, the exact reason for the increase remains unclear. It is also possible that a change in people’s beliefs around anti-depression medication, and an increased acceptance that medication is the best treatment for depression, has also in part prompted this change. Therefore, it may be a difference in the meaning that people attribute to anti-depression medication, that has led to this increase.

It is not just the meaning that people attribute to a tablet that is capable of having an effect. An example of the meaning people attribute to the mode of delivery of a medication is shown in a study that compared placebo injections to placebo tablets (de Craen *et al.* 2000). In de Craen’s study placebo injections were found to be more effective than placebo tablets. This cannot be due to the injection being more effective than the tablet as neither included an active ingredient, rather it is to do with the meaning people attach to injections that led to the effect. In addition the colour of the tablet and the number of tablets given has been shown to affect the placebo response (Blackwell, Bloomfied and Buncher 1972). This study found that blue capsules produced a greater sedative effect than pink capsules and the effect of two capsules was greater than the effect of one capsule. Blackwell and de Craen’s studies provide a useful insight into some of the complexities of the placebo effect.

Practitioners style of delivery can also influence the impact of the placebo effect (Thomas 1987). This is of particular relevance to treatments such as homeopathy, where the practitioner may be perceived to be a major contributor to any effectiveness. A study was carried out in 1984 (Thomas 1987) where patients visiting a GP surgery with symptoms, but without abnormal physical signs, were randomised to one of four consultations: a consultation carried out in a positive style (with or without treatment) or a consultation carried out in a in a “non-positive” style (with or without treatment). A positive style involved the GP giving the patients a firm diagnosis and assuring them that they would get better within a few days. If the patient was given a medication they were told that it would definitely make them better. If they were not given a medication they were told that in the doctor’s opinion they did not require any medication. The negative style consultation was an artificial consultation where the GP stated; “*I cannot be certain what is the matter with you”*, and if no prescription was given the GP added; *"And therefore I will give you no treatment.*" If however a prescription was given GP added, *"I am not sure that the treatment I am going to give*

you will have an effect" (Thomas 1987) page 1200. The consultation closed with the GP telling the patient to return if they were not better in a few days. In all cases the treatment given was a placebo tablet, i.e. no one in the study received an active medication. After the consultation with the doctor, patients were asked to fill in a patient satisfaction survey, answering four questions designed to gauge patient satisfaction (the exact questions are not reported). Two weeks after the consultation patients were sent a questionnaire asking the following three questions: Did you get better? How many days after seeing the doctor did you get better? Did you require any further treatment? The study found that patients who received a positive consultation were more likely to get better than those who didn't. In this study only one doctor, who was also the researcher, delivered the consultations. In addition, the outcome measures used were not validated. This leads to the possibility that the findings are not generalisable. Whether or not the patient was prescribed a tablet made no difference to whether or not the patient got better (53 out of 100 who received a tablet, compared to 50 out of 100 who didn't receive a tablet), which is interesting in itself. However the tablet was not the focus of the article and the effect of being prescribed a tablet is only briefly discussed. Despite this, this study does show that, in the case of this particular doctor, varying the style of consultation, led to differing patient outcomes. Thomas's study provides an example of how the meanings attached to a treatment, such as the hope instilled in the patient by the practitioner, can have a strong effect. Each patient-practitioner interaction is unique, and therefore the strength of the patient-practitioner interaction, and what it means to the patient is impossible to determine in advance. Furthermore the meaning the patient attaches to the interaction and therefore the so called "placebo effects" of the consultation, will depend on the attitude of the prescriber towards the treatment and towards the patient, along with the attitude of the patient towards the prescriber, the treatment and towards their own health (Moerman 2002).

Therefore although placebo medications are inert substances that cannot do anything biologically themselves, it is feasible that the meaning that people attach to them is capable of having an effect (Moerman and Jonas, 2002). In light of this the next section moves away from the term placebo and discusses other possible ways of viewing the placebo effect.

2.6.1 Meaning response

With the term placebo comes the connotations of deception and hypochondria, connotations that are unhelpful in understanding how and why something inactive should have an effect. In addition, the lack of coherence in defining the nature of what placebo is and isn't only leads to contradictions and confusion (Gotzsche, 1994). Moving away from the term "placebo", with all its connotations of deception and lack of effectiveness, coupled with the lack of theorising about placebo's mechanism of action, seems helpful when thinking about complex interventions such as homeopathic treatment. Instead of the terms "placebo" and "placebo effect", Moerman uses the term "meaning response", implying that it is the meanings that people attribute to things that lead to any effects. "Meaning response" is a more helpful term because it is starting to provide an explanation as to why something apparently "inactive" should have an effect; that is, because of the meanings people attribute to it. Paterson and Dieppe, however prefer the terms characteristic and incidental effects (Paterson and Dieppe 2005). Characteristic or specific effects are those that are unique to a specific therapy and believed to cause the outcome. Incidental or non-specific effects are other factors that are thought to affect the outcome e.g. patient expectations, credibility of treatment, therapeutic alliance etc. (Paterson and Dieppe 2005). It is also possible to think not of placebo and placebo effects but of context effects (Di Blasi *et al.* 2001). Context effects are factors that may influence a patient's response to a treatment such as the setting, aspects of the practitioner (personality, status, sex etc.), treatment characteristics (mode of delivery, colour or shape of tablet etc.) or patient's characteristics (beliefs about illness, degree of anxiety etc.). Thinking in terms of context effects allows for the fact that context effects will vary depending on the context of the treatment, and that there is not a single mechanism of action for these effects. For example the strength of the context effects for a given treatment will depend on who is providing the treatment, their manner and demeanour, what the treatment is like, is it a tablet or an injection, what colour is it, where is it delivered, in a GP surgery, in hospital or at home. All these factors can influence the context effects and lead to different outcomes (Moerman 2002). The terms context effects, meaning response and non-specific effects, provide a more accurate portrayal of effects that are non-specific to the treatment than the terms "placebo" and "placebo effect." This is because these alternative terms do not have the unhelpful connotations of deception and lies associated with the word placebo. Such connotations can lead to the belief that a person

who gets better after receiving a placebo is likely to be a hypochondriac, and thus to the conclusion that there is little value in investigating the “placebo effect” and possible mechanisms of action. However, non-specific factors can lead to an improvement in a person’s condition or illness despite their not having any intrinsic biological activity, and although they do not have an intrinsic biological activity, it does not mean that biological effects will not be observed (Moerman 2002).

In order to isolate what is unique to a therapy and what is not, it is helpful to look at the terms “unique elements”, and “essential but not unique elements”. Waltz used these terms in her work on assessing adherence to treatment and therapist competence in psychological therapies (Waltz *et al.* 1993). Although Waltz used the terms as a means to describe therapist behaviours when conducting a treatment, they can equally be applied to elements of the treatment itself rather than solely therapist behaviours. An example of an essential but not unique aspect of a treatment would be in the case of IHT, the interaction with an empathic practitioner. Many treatments involve a consultation with an empathetic practitioner, therefore it is not unique, however without the interaction with an empathetic practitioner it would be difficult, if not impossible, to obtain the information needed to prescribe a homeopathic remedy.

To summarise, placebos and the placebo effect are labels used to describe the observation that biologically inactive treatments can lead to an improvement in symptoms. Simply using the label “placebo” does not explain how these improvements occur. It is more meaningful to use other terms such as “context effects”, “meaning response”, “specific” and “non-specific” effects or “unique” and “essential but non-unique” elements rather than “placebo” because these terms do not have any of the negative connotations associated with the term “placebo”.

2.7 ‘Unique’ and ‘essential but non-unique’ elements of homeopathic treatment

In order to explore the concept that homeopathic treatment is a placebo treatment, it is useful to understand what the “unique” or specific effects and the “essential but non-unique” or “non-specific” effects of homeopathic treatment are. To do this a search was carried out in October 2009; this search was repeated in May 2010 and June 2012.

The search was carried out in Web of Science (1898-2012), AMED (Allied and Complementary Medicine) 1985 to June 13 2012, Embase (1947 to June 13 2012), Ovid MEDLINE(R) (1950 to June Week 1 2012), and a database of homeopathy trials up to 1995 (Dean 2004), using the key words “specific effect”, “context effect”, “non specific effect”, “homeopath*” and the MeSH term homeopathy, (full details given in Appendix 1).

The titles and abstracts of the studies identified by the searches were read to determine whether they were exploring the specific, and/or non-specific, effects of homeopathic treatment. The full text of all studies that mentioned specific or non-specific effects in relation to homeopathic treatment were accessed. Studies which talked about non-specific or specific effects with relation to plants, animals or laboratory research into ultra high dilutions were excluded. There were twelve potentially relevant studies, however only one of these had attempted to classify the non-specific and specific elements of homeopathic treatment. This was a study by Thompson (Thompson 2006), which on reading was found to be reporting the results of an earlier study (Thompson and Weiss 2006) that looked into the active ingredients in homeopathic treatment. Three of the other studies were RCTs (Brien, Lachance and Lewith 2004; Fisher *et al.* 2006; Adler *et al.* 2011), these RCTs attempted to measure specific and/or non-specific effects of homeopathic treatment rather than characterising these effects and are discussed in Chapter 4. Also identified were five discussion pieces on trials of homeopathic treatment and how to explore whether homeopathic treatment exerted a specific effects (Vickers 2000; Weatherley-Jones, Thompson and Thomas 2004; Ernst and Canter 2005; Mathie 2006; Ernst 2011), two reviews of the effectiveness of homeopathic treatment (Shang *et al.* 2005; Clausen, van Wijk and Albrecht 2011) and a trial assessing a homeopathic complex for menopausal symptoms (Wasilewski 2004).

In Thompson’s study participants were offered a package of care which consisted of five homeopathic consultations. Prior to the initial consultation, and following the final consultation, participants were interviewed. At the initial consultation the interviews focused on patient expectations and the final interview focused on understanding patients’ experiences. All consultations were recorded and transcribed. At the end of treatment, data such as questionnaires (disease specific, Measure Yourself Medical Outcome Profile, Glasgow, Homeopathic Hospital Outcome Profile and Consultation and Relational Empathy Scale) and a report from a “significant other" were collected. In addition to this, participants were asked to produce

a piece of artwork that depicted their treatment. Textual data was analysed using thematic analysis, with themes being either pre-existing, derived from previous theoretical study, or emerging from the data. Triangulation of the interview data, questionnaires, artwork and report from significant other was used to create an informal composite measure which the author termed “global outcome assessment.” Whilst triangulating the data in this way provides a useful way of assessing patients in terms of taking all the available data into account, no discussion is provided on how conflicting views were dealt with. This leads to a question over the thoroughness of the triangulation, as it is unlikely that all the data would be in agreement. The global assessment placed each participant into one of three categories; major, some or none. These categories related to the degree of improvement each participant had experienced in relation to their health status over the treatment period. The exact details of the analysis and triangulation are not reported and nor is how the active ingredients were identified, save to say that the analysis process was guided by a text by Mason (Mason 1996).

The focus of the report is on the active ingredients of interest that emerged though the analysis process. Some of these active ingredients can be thought of as generic, such as consultational empathy and some specific to homeopathic treatment, such as the remedy matching process. Whilst not trying to propose that the effects covered identified all the different modes of action, Thompson’s study provides a framework for exploring the potentially therapeutic factors of homeopathic treatment. Whilst, there is a lack of detail given on the analysis method, there is a detailed description of the results for two of the patients is given by Thompson, one of whom achieved a major improvement and one who remained the same. The description used illustrations from the different data generated for these patients to show how the data fitted together and how it fitted with the overall global assessment for each of the two patients. These illustrations provided a convincing account of how these patients improved or didn’t improve through treatment. This, coupled with the detailed descriptions of the active ingredients, backed up by examples from a variety of the 18 patients who took part in this study and an honest description of the study’s limitations, lead to the decision that this is a credible study. This is one of the first studies to open the “black box” of homeopathic treatment and whilst it may not have identified all the potential therapeutic effects, it gives a useful overview of what these effects may potentially be. Specific effects of homeopathic treatment were characterised by Thompson et al as;

- In depth enquiry into bodily complaints and idiopathic symptoms
- Homeopathic remedy
- Remedy matching process.

Non-specific effects can be characterised as;

- Consultational empathy
- Openness to mind body connection
- Disclosure

Exactly how these effects were categorised is not entirely clear. Despite this the above lists provide a useful framework for looking at what is specific or non-specific to homeopathic treatment. This is because the elements are clearly defined and can thus be used when exploring what is specific and non-specific to homeopathic treatment.

In summary, this chapter has explored some of the concepts relevant to homeopathic treatment such as placebo, specific and non-specific effects. It has also explained why evaluating the effectiveness of homeopathic treatment is important within the context of homeopathic treatment remaining available on the NHS. In light of the importance in evaluating the effectiveness of homeopathic treatment the next chapter describes a systematic review into the effectiveness of homeopathic treatment for irritable bowel syndrome.

3 Systematic review of homeopathic treatment for irritable bowel syndrome

The previous chapter highlighted the reasons why it was important to evaluate the effectiveness of homeopathic treatment. However before deciding whether or not a trial of homeopathic treatment for irritable bowel syndrome (IBS) is needed, it is useful to review the current evidence for homeopathic treatment for IBS. In light of this a scoping search was carried out to assess the current available information, prior to carrying out a systematic review. This chapter discusses the reasons why a systematic review of the effectiveness of homeopathic treatment for IBS was carried out and the methodology and methods used, before moving on to discuss the results of the systematic review.

3.1 Introduction

The Cochrane systematic review reported in this PhD thesis was carried out simultaneously with the RCT trial. Ideally the systematic review would have been carried out in advance of the RCT and the results of the systematic review used to inform the development of the RCT. However due to time limitations this was not possible. Instead an early scoping search was carried out prior to the RCT to assess the available information on homeopathic treatment for IBS. This scoping search is described in the next section. It is necessary to conduct a search of the literature prior to carrying out a research project because it would be unethical to conduct research in an area where there was already a clear answer in the literature (World Medical Association 2008). This means that it is necessary to demonstrate that there is a clear need for a study prior to its commencement. Hence a scoping search to assess the available information on homeopathic treatment for irritable bowel syndrome was carried out prior to conducting the RCT. The aim of the scoping search was to determine what the available evidence was of the effectiveness of homeopathic treatment for IBS to allow a decision to be made as to whether or not there was need for a trial exploring the effectiveness of homeopathic treatment for IBS. If it had been found that there was conclusive evidence for or against the effectiveness of homeopathic treatment for IBS, then there would have been no need for another trial.

3.2 Scoping search on homeopathic treatment for irritable bowel syndrome

The scoping search was initially carried out in November 2009, repeated in May 2010 and again in June 2012. The search was initially carried out in 2009 to determine whether there was a need of a trial of IHT for IBS. It was repeated in 2010 to ensure that the results were accurate and up to date for the application to the research ethics committee. It was repeated again in 2012 for the purpose of writing this thesis, to ensure that up to date results were included.

Searches were carried out in Web of Science (1898-2012), AMED (Allied and Complementary Medicine) (1985 to June 2012), Embase Classic + Embase (1947 to 2012 June 27) and Ovid MEDLINE (1946 to June week 3 2012), a database of homeopathy trials up to 1995 (Dean 2004) and Hom-Inform (the database of the British Homoeopathic Library) using the key words “Irritable bowel syndrome”, “irritable bowel disease”, “irritable colon”, “homeopath*” and the MeSH terms homeopathy and irritable bowel syndrome.

The search strategies are shown in Appendix 2.

References in systematic reviews of homeopathic treatment were also searched.

The abstracts of the identified papers were read, to determine whether or not they were a study on the use of homeopathy in the treatment of IBS. The full text of those that appeared to be relevant was then skim read.

These scoping searches identified many discussion papers, single case reports e.g. a clinical audit (Treuherz 1998), one consecutive case series (Gray 1998) and three randomised controlled trials (Owen 1990; Rahlfs and Mossinger 1976; Rahlfs and Mossinger 1979).

In the consecutive patient case series (Gray 1998), 20/25 patients reported an improvement and 14/25 reported marked improvement, judged by decreasing intensity and frequency of their symptoms. A small pilot pragmatic randomised controlled trial (RCT) of homeopathic treatment alone compared to usual care alone (Owen 1990) found no difference between the two arms (n=23). Two RCTs comparing homeopathic medicines to placebo of homeopathic medicines (Rahlfs and Mossinger 1976; Rahlfs and Mossinger 1979) reported positive results. Rahlfs (Rahlfs and Mossinger 1979) found that 32/42 (76%) of those in the homeopathic medicine arm

reported significant relief compared to 18/43 (42%) of those in the placebo arm. Despite these findings as yet no systematic review has been carried out on homeopathy for IBS. As it stands the existing evidence, although patchy, does suggest a need for further research into the clinical effectiveness of homeopathic treatment for patients with IBS. Furthermore there was no Cochrane review registered to study this question.

3.3 Rationale for carrying out the systematic review

One of the reasons for carrying out a systematic review is to summarise the available evidence of effectiveness on a specific topic. Systematic reviews of effectiveness aim to bring together all the evidence of effectiveness (for a treatment(s)), that correspond with predefined exclusion/inclusion criteria for a particular question (Wider and Boddy 2009), e.g.; “Does homeopathic treatment work for irritable bowel syndrome?” Often systematic reviews contain meta-analyses. Meta-analyses involve the use of statistical methods to give an estimate of the overall result by combining the results of individual studies (Glass 1976). This allows a more precise estimate of the overall effect of the intervention to be given rather than simply quoting the results from individual studies (Deeks, Higgins and Altman 2011).

The use of strategies to limit bias and random error mean that systematic reviews are less prone to bias than traditional narrative reviews (Cook, Mulrow and Haynes 1997). Traditional reviews are at risk of providing incomplete or biased information through conscious or unconscious bias in the search procedure and sources used in the review, whereas systematic reviews have several key features aimed at minimising bias and random error. These are:

- They address a clearly stated question
- Search criteria are made explicit and stated in advance
- They use comprehensive searching and retrieval procedures, defined in advance
- Decisions regarding studies relevance and how and why studies were selected for inclusion are clearly given and correspond to predefined criteria
- A rigorous critical appraisal is given of the included studies

A biased review process in an effectiveness review can lead to an over or under estimation of the treatment effect. Furthermore if a review is not

rigorous or clearly reported it can be difficult to assess how useful the results of the review are in practice, and the validity of the results (Cook, Mulrow and Haynes 1997). In a systematic review explicit systematic methods are used with the intention of minimising bias, meaning that decisions are made based on pre-defined criteria. These criteria and methods are stated prior to conducting the systematic review to allow an accurate and objective conclusion to be drawn (Oxman and Guyatt 1993).
There are a number of means by which bias can occur when conducting a systematic review of a CAM intervention, these include; failure to establish a protocol in advance, including studies that only give the desired answer, failure to identify all relevant studies, failing to address the issue of publication bias and imposing language restrictions on included studies. In addition the studies included in the review may themselves be biased, therefore the validity of the findings from each of the included studies should be assessed by assessing their risk of bias and quality of reporting (Green and Higgins 2011), this is discussed in detail in Section 3.6.4.

To minimise the impact of bias by the author, it is vital that the methods used when conducting a systematic review are transparent, documented in advance and the planned methods peer reviewed (Green and Higgins 2011). When the reasons for judgements are not made explicit it is difficult to assess the validity of the methods used and it is possible for the reviewer to intentionally or unintentionally introduce bias. For example by only including studies that provide their desired answer and excluding studies that do not (Oxman and Guyatt 1993). Furthermore it is likely that errors in judgement will be made if results are informally synthesised and methods not made explicit and documented in advance. Oxman and Guyatt found poor consistency of expert ratings of journal articles when systematic and explicit methods were not used (Oxman and Guyatt 1993).

In a systematic review, appropriate steps should be taken to ensure that as far as possible all relevant studies are identified. This is especially important in areas where there is limited research, such as CAM interventions where one missing RCT can significantly affect the overall result (Wider and Boddy 2009). In addition there is the issue of publication bias, where positive results are more likely to get published than negative results (Easterbrook *et al.* 1991). Publication bias occurs in both conventional and CAM journals (Ernst 2007). Some of the means by which publication bias can be minimised is to, as far as possible, locate unpublished works or works situated in the grey literature (Conn *et al.* 2003). Grey literature is literature

that cannot easily be found through conventional channels, such as searching bibliographic databases. This can be because it is not indexed and therefore not picked up by searching of bibliographic databases, or because it is not made widely available. Examples include documents produced and published by governmental agencies and working groups (Alberani, Pietrangeli and Mazza 1990). Possible means of identifying articles in the grey literature are discussed in section 3.5.2. As already mentioned, limiting language of publication can lead to bias (Pham *et al.* 2005) due to failure to include all relevant studies. This can be a particular problem for CAM where a large portion of studies of some interventions, such as acupuncture, are published in languages other than English (Wider and Boddy 2009). This issue is further explored in relation to the systematic review of homeopathic treatment for IBS in Section 3.5.1.

To summarise, the validity of systematic reviews are based on the inclusion of an unbiased sample of relevant studies using *a priori*, transparent, explicit and well document methodology (Juni *et al.* 2002).

Consequently to update the knowledge base of the effects of homeopathic treatment for IBS, on a more robust basis, it was decided to carry out a systematic review. The advantages of a systematic review, over a literature review are those stated above, in that systematic reviews provide an explicit, structured and transparent means of reviewing the literature. This means that they are likely to be freer from bias than a less formal literature review (Oxman and Guyatt 1993). Furthermore there may be trials that had not been picked up by the scoping literature review, and when the evidence base in small, as is often the case for homeopathic treatment, even one missing RCT can change the findings of the review leading to skewed conclusions (Wider and Boddy 2009). A Cochrane systematic review was chosen because it would offer a structured format for carrying out the review and Cochrane also provide training for those carrying out Cochrane reviews. Furthermore a Cochrane review on homeopathic treatment for IBS had not already been carried out and nor was a protocol registered. Therefore this was an opportunity to fill that gap. The protocol for this review has been published (Peckham *et al.* 2012).

3.4 Aim of the review

The aim of the review was to identify and assess previous trials of homeopathic treatment for IBS, to gauge whether or not homeopathic treatment provides an effective means of treating IBS. I.e. does homeopathic

treatment for IBS work. It was also planned to carry out a meta-analysis to combine the result from previous studies and give an estimated effect size. However this would only be possible if sufficiently similar studies were identified. This is discussed in more detail in Section 3.6.5. In addition, if sufficient studies were identified, a sub-group analysis comparing different forms of homeopathic treatment would be carried out. This is discussed in Section 3.6.5.The role of this systematic review in the context of this thesis was to determine whether or not a trial of homeopathic treatment for IBS was needed.

3.5 Methodology

3.5.1 Rationale for inclusion criteria

When considering how to determine which studies to include in the systematic review, The Cochrane Handbook of Systematic Reviews was consulted (Higgins and Green 2011). From reading this and previous systematic reviews of other interventions for IBS (Liu *et al.* 2006; Zijdenbos *et al.* 2009), it was decided that there were five criteria that needed to be defined. These were: the types of studies to be included, the outcome measures to report, the types of participants in the studies, study design and the interventions delivered in the studies.

The initial scoping search only identified three RCTs of homeopathic treatment for IBS, two were published in German (Rahlfs and Mossinger 1976; Rahlfs and Mossinger 1979) and one in English (Owen 1990). From these findings it was not expected that a large number of studies of homeopathic treatment for IBS would be identified. Since two of the previously identified RCTs were in German (Rahlfs and Mossinger 1976; Rahlfs and Mossinger 1979), it is likely that there may be other RCTs published in languages other than English. Since it is desirable to identify as many eligible studies as possible to obtain the most precise result, studies in languages other than English were included in this review. This is because, as already stated, it is possible that even one missing study can lead to a skewed result (Wider and Boddy 2009). Furthermore excluding studies because of their language of publication can lead to language bias (Egger *et al.* 1997). This is particularly the case if positive studies in one language are more likely to be published than negative studies. It has been found that, for CAM interventions, restricting the language of publication can substantially alter the results (Pham *et al.* 2005). In addition to this there can be a difference between countries, in terms of what gets published. It has been

shown that CAM articles published in the highest impact European journals are more likely to have positive outcomes than those published in the highest impact US journals (Sood *et al.* 2007). It is therefore important not to exclude on the basis of where the study was conducted, rather to assess and report whether the study meets the inclusion criteria and then assess its risk of bias and its quality of reporting (Higgins and Green 2011).

In this systematic review it was suggested by the editor for the inflammatory bowel disease and functional bowel disorders review group that non-randomised studies (NRS) should be included. In enthusiasm for conducting the review it was agreed that cohort studies would be included. To be considered as eligible for inclusion, cohort studies needed to be non-randomised comparative cohort studies where IBS patients treated with homeopathy were compared to IBS patients who hadn't been treated with homeopathy and their progress followed. This review did not include retrospective case-series. However on deciding whether solely RCTs and quasi RCTs should be included in a review information on including (NRS) should be sought (Higgins and Green 2011; Reeves *et al.* 2011). The Cochrane Non-Randomised Studies Methods Group (NRSMG) gives the following reasons for including NRS:

- To provide evidence of benefit/harm for interventions where it is impossible to carry out RCTs or where it is extremely unlikely that RCTs have been carried out.
- To provide evidence/harm for interventions where the effects cannot be effectively studied by RCTs because of rare outcomes or outcomes that were not known to be important when existing RCTs had been carried out.
- To explore the evidence for carrying out an RCT by evaluating existing NRS or use the finding of NRS to inform the design of a randomised trial.

In retrospect the reasons listed above are not met, and it may therefore have been wise not to have included NRS in this review, as there are downsides to their inclusion. The main issue with NRS is that biases are likely to be greater than for randomised studies. The principal source of bias in NRS which have comparison groups is selection bias. This occurs when there are differences in the baseline characteristics of individuals in the different intervention groups. It may be these baseline differences that lead to any observed differences in outcomes rather than the intervention; this means

that it is possible to conclude that there is an intervention effect, when really there is not one. It was therefore important for NRS to consider any weakness of the study design, how the study was conducted, and the possibility for selective reporting of outcomes. Of particular concern are NRS studies which do not report having a protocol. It is believed that such studies are more prone to reporting biases. However their inclusion had already been agreed.

Consequently a narrative description will be given of any cohort studies eligible for inclusion; however they will not be included in any meta-analyses. This is because the Cochrane NRSMG recommends that NRS and randomised studies are not combined and that the results are presented separately. This is because results from different study designs are expected to systematically differ, which results in greater heterogeneity between studies (Reeves *et al.* 2011). It was decided at the outset not to carry out a meta-analysis of included NRS alone because there is a greater risk of heterogeneity between NRS than between randomised studies. This is due to NRS being more likely to be methodologically diverse and therefore not suitable for combining (Reeves *et al.* 2011).

In terms of the interventions offered, trials were included where one arm received homeopathic treatment and the other received a placebo or an active comparator treatment, such as usual care. Homeopathic treatment was defined as a treatment which involved the delivery of a homeopathic remedy; where the remedy was given by a homeopath following a consultation or where a homeopathic remedy was given outside of a consultation. It is possible that effectiveness of homeopathic treatment may be related to the type of homeopathic treatment used i.e. classical homeopathic treatment involving a consultation plus a homeopathic remedy may be more effective than when a homeopathic remedy is given without a consultation. Therefore it was planned that if sufficient studies of high enough quality were identified a subgroup analysis comparing these two forms of homeopathic treatment would be carried out. See Section 3.6.5: Data analysis, for more details. It was deemed unlikely that any trials that directly compared different forms of homeopathic treatment would be identified, however if any such trials were identified they would be eligible for inclusion.

Trials of IBS use a variety of outcome measures such as IBS Severity Scoring System (Francis, Morris and Whorwell 1997), Adequate Relief Measure (Mangel *et al.* 1998) and GI Symptom rating Scale (Svedlund,

Sjodin and Dotevall 1988). There is no consensus as to which is the best outcome measure (Bijkerk *et al.* 2003). The majority of the outcome measures used are self-reported and because of the nature of IBS there is not a physical test that indicates its presence or severity. It was therefore decided that to be considered for inclusion, the study must have reduction of global symptoms of IBS as measured by a global IBS symptom score as one of its outcomes. Examples of global IBS symptom measures are (but not limited to): IBS Severity Scoring System (Francis, Morris and Whorwell 1997), GI Symptom rating Scale (Svedlund, Sjodin and Dotevall 1988) or Functional Bowel Disorder Severity Index (Drossman *et al.* 1995).

For the purposes of this systematic review a global IBS symptom score was defined as an outcome measure that asked “overall how would you rate your IBS?” or an outcome measure that asked patients to rate two or more aspects of their IBS (pain, bloating, constipation or diarrhoea symptoms or satisfaction with bowel habit). The rating could either be on a visual analogue scale or through grading the symptoms as good, adequate or poor or similar. It was not required for the scale used to be validated; this is because the earliest published validated global IBS measure is the Functional Bowel Disorder Severity Index (Drossman *et al.* 1995), and therefore requiring the scale to be validated would preclude all studies carried out prior to 1995, which could potentially lead to the exclusion of relevant studies and a subsequent effect on results.

3.5.2 Searches

It was decided to search the following electronic databases, after consultation with a research librarian and the Cochrane IBD and Functional Bowel Disorders Group editor, as being databases likely to contain studies of IBS and/or studies of complementary and alternative medicine:

MEDLINE Ovid (1948-May 2012), EMBASE classic + EMBASE (1947-May 2012), the Cumulative Index to Nursing and Health (CINAHL) and Allied and Complementary Medicine Database (AMED) (1985-May 2012), The Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library, The Cochrane Complementary Medicine Field, The Cochrane IBD/FBD Group Specialised Register, Hom-Inform (2012) (a homeopathy specific database.)

It was anticipated that there would be a significant amount of grey literature on the subject of homeopathic treatment for IBS. The reason for the abundance of grey literature on homeopathy is that often studies of

homeopathic treatment are published in publications that are not included in the major bibliographic databases (Wider and Boddy 2009). This means that there may be studies that are eligible for inclusion into this review that can not be identified via electronic databases such as MEDLINE alone (Benzies *et al.* 2006). Therefore care needs to be taken to maximise the ability to locate such studies. For this purpose other resources that were used for searching included:

- Reference searching where the reference lists for all included studies were scrutinised for more trials.
- Conference abstracts from Digestive Disease Week (DDW) (2007-2011) and the United European Gastroenterology Week (UEGW) (2007-2011)
- A database of the trials of homeopathy (Dean 2004). This database contains studies of homeopathic treatment from 1821 to 1995.
- Personal contact. Where possible the first author of all included studies will be contacted for information regarding any unpublished trials.
- The Homeopath and Homeopathic Links will be hand searched between 2008 - 2011 to determine the likely yield of these journals.

3.5.3 Missing data

The Cochrane Handbook's guidelines for dealing with missing data were followed (Higgins, Deeks and Altman 2011). In the first instance missing data was requested from study authors. When this was not possible because the authors did not have the missing data or the author was not contactable, the assumptions of the methods used to deal with the missing data were explained, i.e. if the methods used to input the missing data required the data to be assumed to be missing at random this was made clear.

In this review missing continuous data was dealt with by using the last result carried forward method (Pocock 1983) and assumptions explained. However where dichotomous data was missing an available case analysis was performed. An available case analysis is where the analysis is confined to those people for whom no data is missing in the variables required for the analysis (Raghunathan 2004). The potential impact of the missing data on the results of the review is discussed in Section 3.5.3.

3.6 Methods

3.6.1 Inclusion criteria

Types of studies and interventions

To be eligible for inclusion into this review studies needed to be randomised controlled trials (RCTs) or quasi-randomised studies that compared homeopathic treatment with placebo or an active comparator e.g. usual care. Or in the case of cohort studies, where a group of people are followed over time, to be eligible studies needed to explore the association between having homeopathic treatment and subsequent outcome by comparing people with IBS who received homeopathic treatment with those who didn't receive homeopathic treatment. The rationale for these inclusion criteria is given in 3.5.1

Rationale for inclusion criteria

All such studies were evaluated for inclusion regardless of publication language and publication status (full / abstract etc). For the purpose of this review quasi-randomised studies were defined as studies that have been randomised using "quasi-random" methods, such as alternation between treatment arms, year of birth or month entered into study (Torgerson and Torgerson 2008).

A narrative description was given of any cohort studies eligible for inclusion; however they were not included in any meta-analyses for the reasons given in 3.5.1.

Types of participant

Participants needed to have been diagnosed with IBS using either the ROME criteria (Drossman 2006) or through clinical symptoms. Trials where greater than 10% of the participants had ulcerative colitis, Crohn's disease or bowel cancer were not included in the review. This was because the symptoms of ulcerative colitis, Crohn's disease and bowel cancer can be similar to the symptoms of IBS leading to the possibility of people being diagnosed with IBS before subsequently going on to being diagnosed with ulcerative colitis, Crohn's disease or bowel cancer. There is no test that confirms a diagnosis of IBS, rather it is diagnosed through the Rome criteria or though physical symptoms in the absence of alarm signs (Drossman 2006). Therefore the symptoms that were supposed as being down to IBS may not have in fact have been down to IBS and there is a possibility that such patients do not, and potentially never did have, IBS.

Outcome measures

The study must report the outcome of global symptoms of IBS as measured by a global IBS symptom score, as one of its outcomes. Examples of global IBS symptom measures are (but not limited to): IBS Severity Scoring System (Francis, Morris and Whorwell 1997), Adequate Relief Measure (Mangel *et al.* 1998), GI Symptom rating Scale (Svedlund, Sjodin and Dotevall 1988), Functional Bowel Disorder Severity Index (Drossman *et al.* 1995) or IBS Symptom Questionnaire (Goka and Sandy 1999). What will constitute a global outcome measure, for the purpose of this review, has been defined in section 3.5.1.

As long as a study had a suitable primary outcome (i.e. a measurement of global symptoms of IBS as defined in section 3.5.1), it was suitable for inclusion regardless of secondary outcomes; however data from eligible studies was also collected on the following secondary outcomes, where possible.

The following were secondary outcomes of interest in the review:

- Quality of life as measured by validated quality of life measure e.g. EQ-5D (Williams 1990), SF36 (Ware and Sherbourne 1992) , IBS Quality of Life Measure (Patrick *et al.* 1998), IBS Quality of Life Questionnaire (Hahn *et al.* 1997), Functional Digestive Disorder Quality of Life Questionnaire (Chassany *et al.* 1999), IBS Health Related Quality of Life Questionnaire (Wong *et al.* 1998);
- Abdominal pain, discomfort and distension
- Stool frequency, bowel transit time
- Stool consistency – self report
- Other global rating scales such as the EQ-5D visual analogue scale
- Adverse events, such as an undesirable event associated with the use of the homeopathic medicine in the study i.e. breathing problems or skin irritation.
- Costs

3.6.2 Searches and search strategy

The following electronic databases were searched in May 2012.

MEDLINE Ovid (1946-May week 2 2012), EMBASE classic + EMBASE (1947-2012 May 24), the Cumulative Index to Nursing and Health (CINAHL) and Allied and Complementary Medicine Database (AMED) (1985-May

2012), The Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library, The Cochrane Complementary Medicine Field, The Cochrane IBD/FBD Group Specialised Register, Hom-Inform (2012) (a homeopathy specific database.)

MEDLINE was searched using the following terms which were modified and then applied to other databases

#1 colonic diseases/ OR irritable bowel syndrome/ OR colonic diseases, functional/ OR irritable bowel[tw] OR irritable colon[tw] OR spastic colon[tw] OR functional bowel disease*[tw] OR functional colonic disease*[tw]

#2 homeopathy/ OR homeopath*[tw] OR homoeopath*[tw]

#3 #1 AND #2

The search strategy did not include a filter for RCTs, or cohort studies. This was because it was not expected that a large number of studies would be identified, and it would thus be feasible to search through all identified studies.

The following sources were also searched:

1. Reference searching. The reference lists for all included studies were scrutinised for more trials.

2. Conference abstracts. Conference abstracts from Digestive Disease Week (DDW) (2007-2011) and the United European Gastroenterology Week (UEGW) (2007-2011) were searched.

3. Other databases. A database of the trials of homeopathy was also searched (Dean 2004). This database contained studies of homeopathic treatment from 1821 to 1995.

4. Personal contact. Where possible the first author of all included studies was contacted for information regarding any unpublished trials.

5. Handsearching. The Homeopath and Homeopathic Links were hand searched between 2008 - 2011 to determine the likely yield of these journals.

3.6.3 Data collection

Studies identified by the literature search were independently reviewed by two people, (the author and a colleague). First we discarded any studies with titles that were obviously not relevant e.g. titles such as homeopathic treatment for ulcerative colitis. Following this we assessed the remaining titles and abstracts against the inclusion criteria. Figure 3-1 shows a flow

diagram of this process. Any disagreements were resolved by a third party (the author's supervisors).

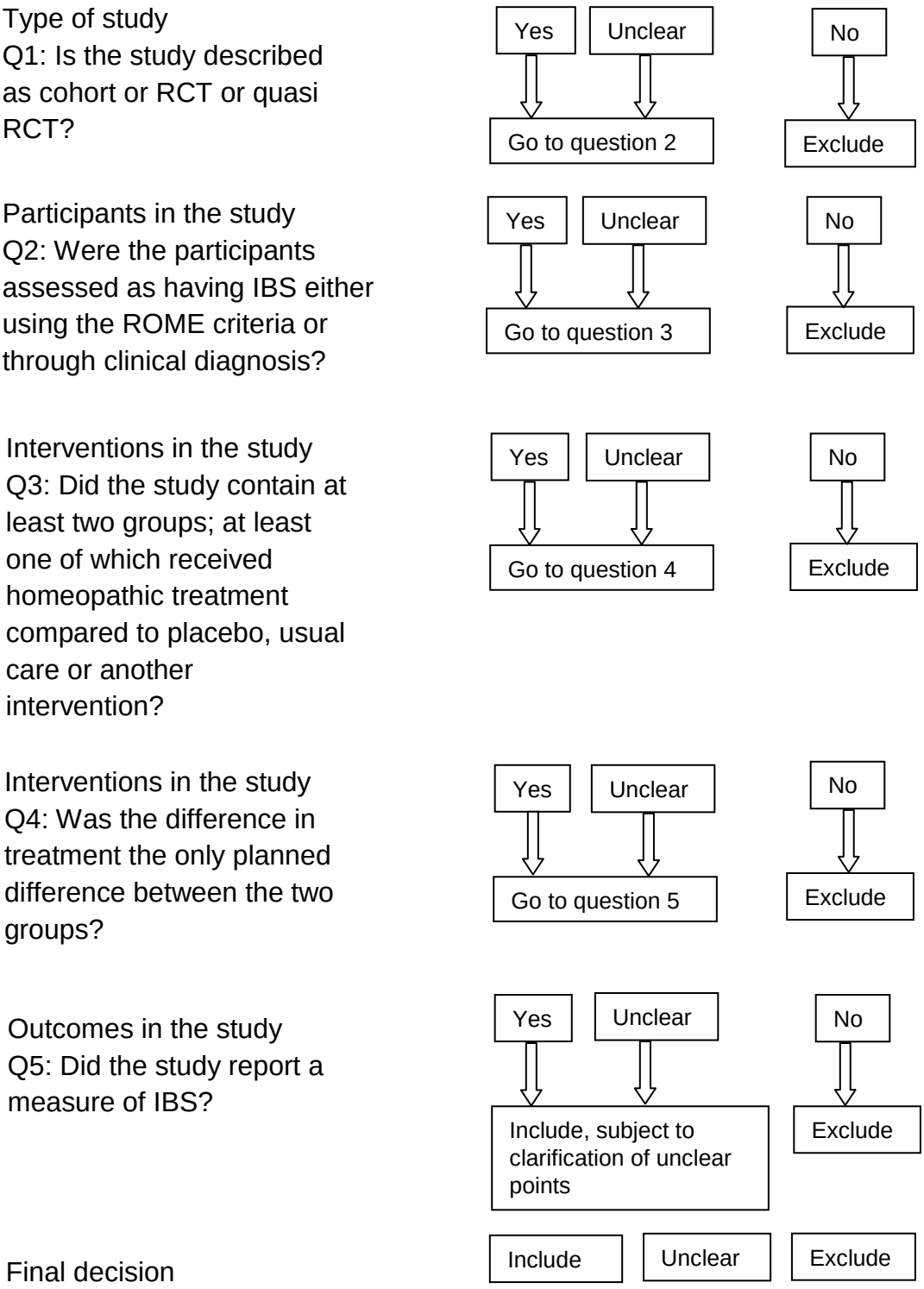

Figure 3-1: Study eligibility flow diagram

Data was extracted from the included studies using a data extraction sheet prepared for this purpose, see Table 3-1 below. Authors were contacted to clarify any unclear data, where possible. The data extraction table was constructed through advice given at the Cochrane Workshop, on reading the Cochrane Handbook (Higgins and Deeks 2011) and the preferred reporting of items for systematic reviews and meta-analyses (PRISMA) (Moher *et al.* 2009). The PRISMA statement was released in an attempt to improve the quality of reporting of systematic reviews. It is important that the data extraction form is transparent and reproducible to enable double checking. Data should be collected on aspects that may influence the outcome or magnitude of effect, such as the type of participants, how participants were diagnosed, setting or intervention used. Data is also required on factors that may introduce different biases such as study design. It is also useful to collect data on aspects of the study that allow others to make a judgement as to the applicability of the review such as, where the study was conducted (geographic location, setting) and details about the participants (age, gender, ethnicity). Finally information on the results obtained in the study needs to be collected to allow a summary to be made of the results of the included studies and if applicable to carry out a meta-analysis (Higgins and Deeks 2011). Table 3-1 was used as far as possible for any cohort studies identified as eligible, however a further table (Table 3-2) was constructed to allow data relevant to NRS to be collected. This table was compiled based on advice from the Cochrane Handbook chapter on non-randomised studies, (Reeves *et al.* 2011) and also the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (von Elm *et al.* 2008). The STROBE guidelines were complied in an attempt to improve the quality of reporting of observational studies. In Table 3-2 answers were reported as yes, no or can't tell as per Cochrane guidelines (Reeves *et al.* 2011).

		Study 1	Study 2
Participants	Description		
	Geographic location		
	Setting (e.g. hospital/private clinic etc)		
	Age (mean, (SD) range)		
	Gender (% female)		
	Ethnicity		
	Inclusion criteria		
	Exclusion criteria		
	Diagnostic criteria (e.g. ROME/clinical/other)		
	Measurement of baseline IBS severity		
Study design	(e.g. randomised controlled trial/cross over/cluster etc)		
	Duration of study		
	How was randomisation achieved (random numbers,		
	Masking (clinicians, patients, assessors)		
Intervention	Description of intervention (e.g. type of homeopathy/details of remedies given/strength/dosage)		
	Details of control		
	Fidelity/integrity checked?		
Outcomes	Primary outcome(s)		
	Secondary outcome(s)		
	Adverse events		
	Time points when outcomes were collected during the study		
	Notes		
Analysis	Analysis method(s) used (intention to treat, per-protocol)		
Missing data	Is missing data reported?		
	How was missing data dealt with?		
Other	Author contacted (Y/N)		
	Power calculation given (Y/N)		

Table 3-1: Data extraction form for included studies

	Study 1	Study 2
Was there a comparison: Between two or more groups of participants receiving different interventions?		
Were participants allocated to groups by: Actions of the researchers? (other than concealed randomisation or quasi-randomisation) Time differences? Location differences? Treatment decisions? Participants' preferences? On the basis of outcome? Some other process? (specify)		
Which parts of the study were prospective/ retrospective (state which): Identification of participants? Assessment of baseline and allocation to intervention? Assessment of outcomes? Generation of hypotheses?		
On what variables was comparability between groups assessed: Potential confounders? Baseline assessment of outcome variables?		

Table 3-2: Data extraction form for NRS

A separate table was used to capture information on the flow of participants through the trial as shown below in Table 3-3. This table was constructed based on the CONSORT guidelines laid out for the reporting of clinical trials of non-pharmacologic interventions (Boutron *et al.* 2005).

Number of participants	Study 1		Study 2	
	Intervention	Control	Intervention	Control
Eligible				
Excluded				
Refused to take part				
Randomised				
Excluded post randomisation				
Withdrawn				
Lost to follow up				
Died				
Included in analysis				
Notes				

Table 3-3: Information on flow of participants

Outcome data was collected for each included study and recorded as shown in Table 3-4 (for dichotomous outcomes) and Table 3-5 (for continuous outcomes.)

Outcome	Timing	Intervention		Control		Notes
		Observed	Total	Observed	Total	

Table 3-4: Outcome data for dichotomous data

Outcome	Timing	Intervention				Control			
		Mean	Mean chge*	Std dev**	N	Mean	Mean chge	Std dev	N

Table 3-5: Outcome data for continuous variables

*Mean chge means mean change

**Std dev means standard deviation

The Cochrane Reviewers Handbook (5.1.0) (Higgins and Green 2011) was referred to for guidance regarding any assumptions made about results, e.g. missing standard deviation, misreporting standard error as standard deviation, and lack of information on withdrawal or loss to follow up.

3.6.4 Assessment of quality

The methodological quality of the included RCT were assessed using the Cochrane risk of bias tool as described by the Cochrane Reviewers Handbook (5.1.0) (Higgins and Green 2011). Each of the sources of bias given below were assessed and graded as either low, high or unclear.

- sequence generation (i.e. was allocation sequence adequately generated?)
- allocation sequence concealment (i.e. was allocation adequately concealed?)
- blinding (i.e. was knowledge of the allocated interventions adequately prevented during the study?)
- incomplete outcome data (i.e. were incomplete outcome data adequately addressed?)
- selective outcome reporting (i.e. are reports of the study free of suggestion of selective outcome reporting?)
- other potential sources of bias (i.e. was the study apparently free of other problems that could lead to a high risk of bias e.g. baseline imbalances, evidence of carry-over in cross-over trials, comparability of groups in cluster trials).

The results from this assessment were tabulated as shown in Table 3-6.

Study ID	Risk of bias	Support for judgement
Lead author and date	(low/high/unclear)	A brief description of why the grading was given e.g. If study was given a high risk of bias for blinding, this box could contain the following " this study was not blinded" or "no description of blinding procedures was given." To explain why the study had a high risk of bias.

Table 3-6: Risk of bias table

The quality of quasi-randomised, non-randomised trials and cohort studies was assessed using a quality instrument designed for assessing the quality of non-randomised studies (Downs and Black 1998). A review of instruments for assessing the quality of non-randomised studies (Deeks *et al.* 2003) concluded that the two most useful tools were those by Downs and Black or

the Newcastle-Ottawa Scale (Wells *et al.* 2008). On assessing the suitability of these two instruments the one by Downs and Black was chosen because it was more comprehensive, containing 27 elements compared to 8 in the Newcastle-Ottawa Scale. In the review by Deeks et al it was suggested that the Newcastle-Ottawa Scale would need some modifications to make the tool suitable for use in effectiveness studies. In addition, the criterion validity of the Newcastle-Ottawa Scale is currently being compared to more comprehensive tools (Ottawa Hospital Research Institute 2011), hence the more comprehensive Downs and Black tool was chosen.

3.6.5 Data analysis

Data was analysed in Review Manager (RevMan 5.1) using available case analysis, with missing data dealt with as described in section 3.5.3: Missing Data. It was intended that if the interventions, controls, outcomes and patient groups were sufficiently similar, then data from individual trials would be combined for meta-analysis. Meta-analysis would not be used if a high degree of heterogeneity (I^2>75%) was detected (Higgins *et al.* 2003). Statistical heterogeneity was assessed using the Chi-square test and the quantity I^2. Chi-square test was considered statistically significant if P≤0.10. Where meta-analysis was deemed appropriate, for continuous variables, when the same scales had been used, the weighted mean difference was calculated. If studies were deemed sufficiently similar but different scales had been used, then the standardised mean difference was calculated. In both cases results were quoted along with 95% confidence intervals. For dichotomous outcomes the pooled risk ratio with 95% confidence interval was calculated. In terms of combining the data, a fixed effect model was used to pool data in the absence of heterogeneity, as defined by an I^2 < 50% and a p value of chi-square of less than 0.10. However, an I^2≥ 50% and less than 75% was considered to represent moderate heterogeneity and in such cases a random effects model was used for pooling the data. When moderate heterogeneity was found to exist between studies for the primary outcome, reasons for this were explored. For each study, clinical heterogeneity was assessed through the description of the setting and homeopathic approach used (e.g. classical or clinical). Study data was summarised using Forest plots, regardless of whether meta-analyses were carried out.

In terms of unit of analysis issues, it was not anticipated that there would be any issues arising from cluster randomisation. This was because the most common study mode for homeopathic treatment is randomisation of

individuals, and it was therefore unlikely that any trials involving cluster randomisation would be identified. Cluster randomisation is where groups of individuals are randomised to the different interventions, rather than the individuals themselves being randomised to the different interventions. Some examples of the groups that could be used in cluster randomisation are medical practice or school. In the case of cluster randomisation by medical practice, all the people attending a particular medical practice will be randomised to the same intervention (Torgerson and Torgerson 2008). However, a more likely scenario which could lead to unit of analysis issues in trials of homeopathic treatment was cross-over trials, which have been used to assess homeopathic treatment (Frei *et al.* 2005). In the case of cross-over trials data was extracted and analysed from the first period only. This is because it is thought that it is likely that there will be a carry-over of the effect of homeopathic treatment (Frei *et al.* 2007). A carry-over effect occurs when the difference between treatments is dependent on the order in which they were given. This can lead to a bias, usually towards the null hypothesis (Higgins, Deeks and Altman 2011). Another possibility where unit of analysis issues could have arisen was where results were reported at multiple time points (Deeks, Higgins and Altman 2011). In this case separate meta-analyses were carried out for each outcome at each time point, when possible. Time points were grouped as follows: less than 3 months and longer than 3 months. These time points were chosen because, through personal experience, and in consultation with other homeopaths, they represent time frames in which a difference in the likelihood of responding would be expected i.e. it is generally thought it will take at least three months to see an improvement in patients receiving homeopathic treatment. Finally in studies where there were multiple intervention groups each intervention group was analysed separately against the control group. In these instances the sample size for the control group was divided proportionately across each intervention group to avoid double counting of the participants in the control group. i.e. if participants in intervention one were compared to the entire control group and participants in intervention two were compared to the entire control group, then the participants in the control group have been analysed twice; once in the comparison between intervention one and the control group and once in the comparison between intervention two and the control group (Higgins, Deeks and Altman 2011).

It was thought unlikely that there would be enough studies of sufficient quality for subgroup analyses to be carried out. However it was intended that if data was reported separately for the different forms of IBS (IBS-D, IBS-C

and IBS-M), then a subgroup analysis to explore whether effect sizes varied across the different IBS subtypes would be carried out. Other subgroup analyses that were intended to be carried out, where possible, were: different homeopathy interventions e.g. classical or clinical and different comparators (e.g. no/usual treatment, placebo, other treatment). Other subgroup analyses could have been considered such as randomisation method (i.e. quasi versus true randomisation). However the greater the number of sub group analyses carried out the greater the chance of a type two error, i.e. a difference is found when there is not really a difference. A fuller discussion on the dangers of multiple analyses can be found in Chapter 7. A sensitivity analysis by quality of studies and randomisation method was to be carried out if a sufficient number of trials were identified. This was to determine if the results of the primary analysis changed according to which trials are incorporated into the analysis, with the quality cut-off point being high risk of bias, i.e. those considered to be at a high risk of bias will be compared to those being of a low or medium risk of bias.

Reporting biases were assessed using funnel plots when more than 10 studies were identified for inclusion in the review (Rothstein, Sutton and Borenstein 2005). Funnel plots are used to check the existence of publication bias and involve plotting, in the form of a scatter plot, treatment effect versus measure of study size. If the plot has an inverted funnel shape then it is unlikely that there is publication bias. However if the shape is asymmetric then this indicates there may be publication bias or systematic differences between the small and large studies, and suggests that an exploration of the cause of this asymmetry is warranted.

3.7 Results

Searches were carried out during the week beginning 21st May 2012. The searches identified 269 studies. Figure 3-2 shows the flow of studies through the screening process.

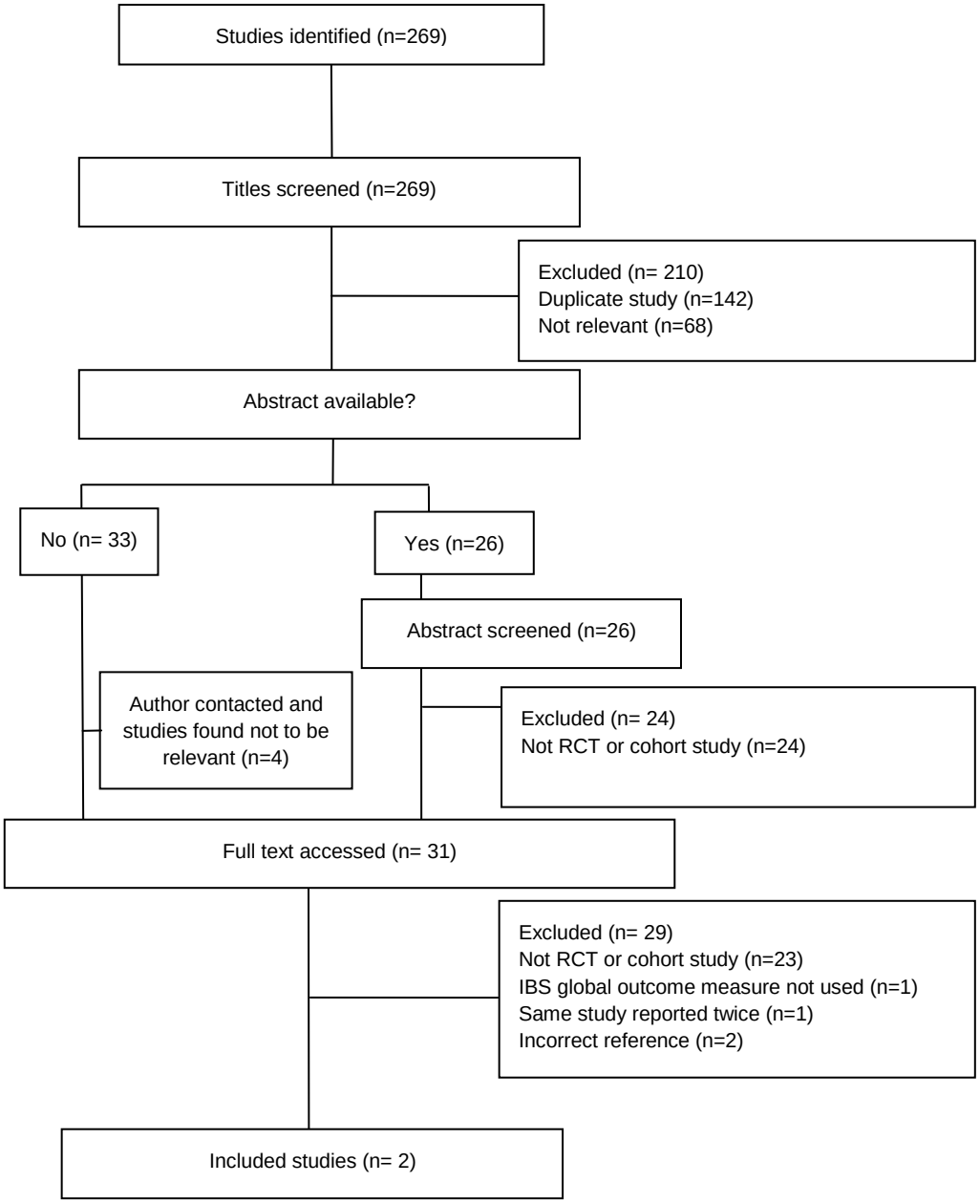

Figure 3-2: Flow of studies through the screening process

After screening titles to remove duplicates 127 studies were left, the remaining titles were screened to remove studies that were obviously irrelevant, leaving 59 studies. Examples of titles of studies considered to be irrelevant were: “Children: young adults or a breed apart?” (Zajac 1998) , “Spring is in the air and the sneezing begins.” (Jones 2005). Of these 59 studies, 26 studies had abstracts. These abstracts were screened and from this 2 of these studies were deemed potentially relevant. However 33 of the studies did not have available abstracts, four of which were written by the same author. This author was contacted and asked about the nature of her studies. They were found not to be relevant to this review being discussion

pieces and treatment strategies. This left 29 studies without abstracts, for which the full text was accessed. This meant that the full text of 31 studies was accessed, the 2 studies that were potentially relevant having read their abstract, and the 29 studies that did not have an abstract available. Having accessed the full text of all potentially relevant articles 3 RCTs were found. No cohort studies were located. Although Owen's (Owen 1990) study was an RCT it did not use a global IBS outcome as its primary outcome. Instead patients were asked to grade their own worst four symptoms on a visual analogue scale. Patients scored the same four symptoms identified at baseline on each of their repeat questionnaires. As these symptoms did not have to be IBS related, this outcome was not a global IBS measure, and therefore this study was not eligible for inclusion. This left 2 RCT trials. Table 3-7 gives details of the studies which were excluded after their full text was accessed along with reasons for their exclusion.

Author	Reasons for exclusion
(Anonymous 2005b)	Not RCT, cohort or study
(Anonymous 2009)	Not RCT, cohort or study
(Aleem 2000)	Not RCT, cohort or study
(Bhagat 2010)	Not RCT, cohort or study
(Bhattacharjee 2010)	Not RCT, cohort or study
(Chimthanawala 2004)	Not RCT, cohort or study
(Diamond and Diamond 2005)	Not RCT, cohort or study
(Feldhaus 2000)	Not RCT, cohort or study
(Gamble 2008)	Not RCT, cohort or study
(Gebhardt 1988)	Not RCT, cohort or study
(Gray 1998)	Case series with no comparison group
(Greeson *et al.* 2008)	Not RCT, cohort or study
(Innes, Greenfield and Hunton 2000)	Discussion on the use of case study methodology with examples of its use using homeopathic treatment
(Jagose 2004)	Not RCT, cohort or study
(Jones 1996)	Not RCT, cohort or study
(Jones 1997)	Not RCT, cohort or study
(Jones 1999)	Not RCT, cohort or study
(Krishendu 2010)	Not RCT, cohort or study
(Lecoyte *et al.* 1993)	Reporting results of same study as reported by Owen 1990.
(Lobo 2000)	Not RCT, cohort or study
(Master 2010)	Not RCT, cohort or study
(Mohan, Kishore and Ratna 2006)	Not RCT, cohort or study
(Owen 1990)	RCT of homeopathic treatment compared to usual care. Outcome measure used was not a global IBS measure
(Pinto 1999)	Not RCT, cohort or study
(Slade 2003)	Not RCT, cohort or study
(Turner 2008)	Not RCT, cohort or study
(White 1999)	Not RCT, cohort or study

Table 3-7: Characteristics of excluded studies

3.7.1 Included studies

Two studies were identified as eligible for inclusion. They were both conducted by Rahlfs and Mössinger (Rahlfs and Mossinger 1976; Rahlfs and Mossinger 1979), both these studies were in German and therefore required translation from German into English, which was carried out by a colleague able to read in German. The 1976 study compared a homeopathic dilution of asafoetida (0.1%), a homeopathic dilution of asafoetida (0.1%) plus nux vomica (0.01%) and placebo. The 1979 study was a repeat of the 1976 study, this time without the inclusion of the asafoetida plus nux vomica arm. It therefore compared asafoetida (0.1%) with placebo. Both of the studies were multi-centre randomised controlled trials carried out in Germany, recruiting patients from general practice who presented with symptoms indicative of IBS. Diagnosis was made through clinical symptoms. No baseline measurements were given, other than the number of males and number of females in each of the arms. The outcome measure for Rahlfs and Mössinger 1976 (Rahlfs and Mossinger 1976) was a global assessment of symptoms at 8 and 15 days. This was a three point scale with the patients scoring whether they were: no better, more than 50% improved, or free of symptoms. Other outcomes were: the day that they felt improvement and an index number generated from patients' symptoms. The outcome measure for Rahlfs and Mössinger 1979 (Rahlfs and Mossinger 1979) was a global assessment of symptoms at 8 and 15 days based on a four point scale, with participants rating whether they were worse, no better, more than 50% improved or free of symptoms. Other outcome measures were the day they felt improvement. A summary of the study characteristics is given in Table 3-8 and Table 3-9 for Rahlfs and Mössinger 1976 and Rahlfs and Mössinger 1979 respectively.

Rahlfs and Mössinger 1976		
Participants	Description	Patients presenting in general practice with symptoms indicative of IBS.
	Geographic location	Germany
	Setting (e.g. hospital/private clinic etc)	GP surgeries
	Age (mean, (SD) range)	Asafoetida 42.81* Asafoetida + nux vom 33.00 Placebo 44.61 *SD and range not presented
	Gender (% female)	50.79%
	Ethnicity	Not stated
	Inclusion criteria	Age 20-60 Pain in abdomen sensitive to palpation plus any three of the following: Pain cutting or stabbing Pain independent of food intake Pain occurring at intervals Flatulence Constipation or regular use of laxatives Emotional disturbance Respiratory problems due to pain in chest Sensitive to fruit, vegetables, legumes, onions or cabbage
	Exclusion criteria	Pathological urine findings Suspected kidney stones Taking long term medication (sleeping tablets and laxatives allowed) Pregnant women Suffered with compliant less than 14 days
	Diagnostic criteria (e.g. ROME/clinical/other)	Clinical
	Measurement of baseline IBS severity	No

Rahlfs 1976 and Mössinger cont/...		
Study design	(e.g. randomised controlled trial/cross over/cluster etc)	RCT multi-centre
	Duration of study	15 days
	How was randomisation achieved (random numbers,	Random balanced code given to each recruiting centre, the exact details of which are not stated. The method of allocation is not clearly described.
	Masking (clinicians, patients, assessors)	Clinicians and patients masked for the allocation, not stated whether assessors were masked for the assessment.
Intervention	Description of intervention (e.g. type of homeopathy/details of remedies given/strength/dosage)	Clinical homeopathy, either: Asafoetida 0.1% in alcohol 6 x 5 drops daily Mixture of Asafoetida 0.1% plus nux vomica 0.01% in alcohol 6 x 5 drops daily.
	Details of control	Placebo solution 45% alcohol 6 x 5 drops daily
	Fidelity/integrity checked?	Not mentioned, however two centres were removed from analysis for not complying with the protocol.
Outcomes	Primary outcome(s)	Self assessment on 3 point scale, no/negligible improvement, more than half improved or free of symptoms
	Secondary outcome(s)	Day number they felt considerable improvement Patient's individual symptoms from which an index number could be calculated,
	Adverse events	None reported

Rahlfs 1976 and Mössinger cont/...		
Outcomes	Time points when outcomes were collected during the study	8 days and 15 days
	Notes	
Analysis	Analysis method(s) used (intention to treat, per-protocol)	Per-protocol
Missing data	Is missing data reported?	Details of why people were not included in the analysis are given however which arm they were in and is not recorded
	How was missing data dealt with?	No discussion on how the missing data was dealt with other than it was not included
Other	Author contacted (Y/N)	N
	Power calculation given (Y/N)	It is claimed in the publication that a power calculation carried out but details not given

Table 3-8: Characteristics of Rahlfs and Mössinger 1976

Rahlfs and Mössinger 1979		
Participants	Description	Patients presenting in general practice with symptoms indicative of IBS.
	Geographic location	Germany
	Setting (e.g. hospital/private clinic etc)	GP surgeries
	Age (mean, (SD) range)	Asafoetida 42.75 (13.21) Placebo 42.33 (10.99)
	Gender (% female)	68.5%
	Ethnicity	Not stated, although one of the exclusion criteria was being "Ausländer". This can be translated as being a foreigner and can be used to include naturalised immigrants, therefore it is likely that participants were all German, however without this being specifically stated it cannot be certain.
	Inclusion criteria	20-60 years Pain in abdomen sensitive to palpation (pain sensitive site must be indicated) plus any three of the following: Pain cutting or stabbing Pain independent of food intake Pain occurring at intervals Flatulence Constipation or regular use of laxatives Emotional disturbance Respiratory problems due to pain in chest Sensitive to fruit, vegetables, legumes, onions or cabbage

Rahlfs and Mössinger 1979		
Participants	Exclusion criteria	Migrant workers and foreigners Pathological urine findings Suspected kidney stones Taking long term medication (sleeping tablets and laxatives allowed) Pregnant women Gallstones and gall bladder problems
	Diagnostic criteria (e.g. Rome/clinical/other)	Clinical
	Measurement of baseline IBS severity	No
Study design	(e.g. randomised controlled trial/cross over/cluster etc)	RCT multi-centre
	Duration of study	14 days
	How was randomisation achieved (random numbers,	Not described
	Masking (clinicians, patients, assessors)	Clinicians and patients masked for the allocation, not stated whether assessors were masked for the assessment.
Intervention	Description of intervention (e.g. type of homeopathy/details of remedies given/strength/dosage)	Clinical homeopathy, Asafoetida 0.1% in alcohol 6 x 5 drops daily
	Details of control	Placebo solution 45% alcohol 6 x 5 drops daily
	Fidelity/integrity checked?	
Outcomes	Primary outcome(s)	Self assessment on a four point scale; worse, not improved/negligible improvement, more than half improved, free of complaint
	Secondary outcome(s)	If they were improved day on which improvement was felt.

Rahlfs and Mössinger 1979 cont/..		
	Adverse events	1 person had Crohn's disease 1 person had heartburn and flatulence 1 person had facial neuralgia 1 person had diarrhoea 1 person had unspecified incompatibility with medication 1 person had severe pain and diarrhoea 1 person complained of tiredness
	Time points when outcomes were collected during the study	8 days and 15 days
	Notes	
Analysis	Analysis method(s) used (intention to treat, per-protocol)	Per-protocol
Missing data	Is missing data reported?	Details of why people were not included in the analysis is reported
	How was missing data dealt with?	No discussion on how the missing data was dealt with other than it was not included
Other	Author contacted (Y/N)	N
	Power calculation given (Y/N)	Power calculation carried out but details not given

Table 3-9: Characteristics of Rahlfs and Mössinger 1979

The participant flow through the studies in shown in Table 3-10. It can be seen that the participant flow was not adequately reported in either of the trials. The number of eligible people is not reported at all, and of the number randomised, only the total number randomised is given. It is not stated how many people were originally randomised to each arm of the trial. These studies were carried out in the 1970s before the CONSORT statement was issued (Schulz *et al.* 2010), which may account in part for the lack of detail on participant flow through the studies.

Number of participants	Study 1			Study 2	
	Asa foetida	Asa foetida + nux vom	Control	Asa foetida	Control
Eligible	NS*	NS	NS	NS	NS
Excluded	NS	NS	NS	NS	NS
Refused to take part	NS	NS	NS	NS	NS
Randomised	72 in total**			119 in total**	
Excluded post randomisation	9 in total**			24 in total**	
Withdrawn				3	3
Lost to follow up	3 in total**			4 in total**	
Died	0	0	0	0	0
Included in final analysis	21	19	23	42	43

Table 3-10: Participant flow for included studies

*NS = not stated

** breakdown by allocation not given.

3.7.2 Risk of bias

As already stated the quality of reporting in the two included studies was poor, this led to difficulty in reporting the risk of bias because the information needed to determine the risk of bias was not available for the majority of areas of possible bias as shown in Table 3-11.

Study ID		Risk of bias	Support for judgement
Rahlfs 1976 and Mössinger	Random sequence generation	Unclear	A chance code was used for the randomisation, the exact nature of which is not reported. Therefore its risk of bias cannot be determined.
	Allocation concealment	Unlcear	Medication was provided in sequentially numbered drug containers but method of allocation is not clearly described.
	Blinding of participants and personnel	Unclear	Study participants and recruiting doctors were blinded, however it is not clear whether or not the assessors were blinded.
	Blinding of outcomes	Unclear	It is not reported whether or not the outcome assessment was carried out blind.
	Incomplete outcome data	Unclear	Insufficient reporting of attrition, reasons for attrition but not details of allocation are given.
	Selective reporting	Unclear	Insufficient information provided.
	Other bias	Unclear	Insufficient information provided to assess whether the study is at risk from other bias.
Rahlfs and Mössinger 1979	Random sequence generation	Unclear	Although it is stated that this is a randomised trial no details are given as to how randomisation was achieved.
	Allocation concealment	Unlcear	Medication was provided in sequentially numbered drug containers but method of allocation is not clearly described.
	Blinding of participants and personnel	Unclear	Description is given as to blinding of participants and doctors, but it is not clear as to whether assessors were blinded.
	Blinding of outcomes	Unclear	It is not reported as to whether the outcome assessment was carried out blind.
	Incomplete outcome data	Low	Missing outcome data balanced in numbers and for missing for similar reasons across all groups.
	Selective reporting	High	28 participants could not be evaluated because of violation of the protocol, however several patients older than the specified inclusion criteria were included in the analysis.
	Other bias	Unclear	Insufficient information provided to assess whether the study is at risk from other bias.

Table 3-11: Risk of bias table for included studies

The random sequence generation was not adequately reported in either of these two studies, although it is stated that a chance code was used in Rahlfs and Mössinger 1976 (Rahlfs and Mossinger 1976); what this entailed is not described. Rahlfs and Mössinger 1979 (Rahlfs and Mossinger 1979) states that it was a randomised trial, but the exact means by which randomisation was achieved is not mentioned. In terms of allocation concealment, in both studies it is stated that the medication was provided in sequentially numbered containers. In Rahlfs and Mössinger 1979 (Rahlfs and Mossinger 1979), the fact that the asafoetida solution had a slight garlicky after-taste is mentioned. It then goes on to describe how, even though the placebo solution doesn't have this, it is unlikely that participants would be able to identify which arm they were in because of the after-taste. This was because asafoetida was not a known medicine at the time of the trial. Therefore participants would have no expectations as to whether or not the medication would have a taste. In addition this was not a cross over trial so participants were only given one medication and therefore would not know about the difference in taste. Finally it is claimed that participants would not have contact with each other during the study. However the possibility that people may have talked to each other while in the waiting room at the doctor's surgery cannot be ruled out.

This thorough description of the blinding of participants to the medication is in contrast to the rest of the reporting of the blinding of outcome assessment, of which nothing is mentioned about whether or not it was carried out blind. This was true of both studies. Although Rahlfs and Mössinger 1976 (Rahlfs and Mossinger 1976) reported some of the reasons for missing outcome data, this was not consistent, making it difficult to tell if the study was at risk of selective reporting bias. However Rahlfs and Mössinger 1979 (Rahlfs and Mossinger 1979) was more thorough in its reporting of missing outcome data and why some participants data was missing. Furthermore the missing data appeared to be evenly balanced across the groups, with a similar number and similar reasons for missingness across the two arms. It is stated in the Cochrane Handbook that an answer of "yes" to there being a similar number and similar reasons for missingness across all arms, can indicate a low risk of bias (Higgins, Altman and Sterne 2011). In terms of selective reporting, this could not be assessed for Rahlfs and Mössinger 1976 (Rahlfs and Mossinger 1976). However Rahlfs and Mössinger 1979 (Rahlfs and Mossinger 1979) was deemed to be at a high risk of bias because there appeared to be inconsistency in exclusion of participant data, in that, whilst some people were excluded for not meeting the inclusion criteria, people

who did not meet the inclusion criteria because they were too old were still included in the analysis. Finally the possibility of other sources of bias could not be determined again due to the inadequacy of reporting in these two studies. In terms of the overall risk of bias for the outcome of improvement in IBS symptoms it is unclear for Ralhfs and Mössinger 1976 (Rahlfs and Mossinger 1976) and high for Rahlfs and Mössinger 1979 (Rahlfs and Mossinger 1979), this is because the risk of bias was unclear for all the domains in Rahlfs and Mössinger 1976 (Rahlfs and Mossinger 1976). For Rahlfs and Mössinger 1979 (Rahlfs and Mossinger 1979) there was a high risk of bias because the risk of selective reporting was deemed to be high as already discussed (Higgins, Altman and Sterne 2011).

3.8 Analysis of results

Data was analysed in RevMan (The Cochrane Collaboration 2011).

Rahlfs and Mössinger 1976 (Rahlfs and Mossinger 1976) and Rahlfs and Mössinger 1979 (Rahlfs and Mossinger 1979) reported outcomes at both 8 and 15 days. For the data analysis, data was taken at the study endpoint of 15 days. Although it was planned that where there was missing continuous data, a last value carried forward method would be used to input the missing data, in practice this could not be done. This was because baseline data was not given for any of the participants, and furthermore there was no way of matching up missing 15 day scores with their corresponding 7 day scores. In a further point, in the text of Rahlfs and Mössinger 1979 it states that data was collected at 7 and 14 days, however in the tables where the data is reported, it states that the data was collected at 8 and 15 days. Whilst this discrepancy was noted it was considered that whether or not the data was collected at 14 or 15 days would make little difference to the overall result.

Rahlfs and Mössinger 1976 (Rahlfs and Mossinger 1976) was a three armed trial, with two different homeopathic treatments being compared to placebo. This could have led to unit of analysis issues. To prevent this the number of participants in the placebo arm was divided by two, as explained in Section 3.6.5. This meant that two comparisons were entered into RevMan: asafoetida (0.1%) compared to placebo and asafoetida (0.1%) + nux vomica (0.01%) compared to placebo. The results for the outcomes are shown in Table 3-12.

The two studies were deemed sufficiently similar to carry out a meta-analysis. This was because they had used the same outcome, in addition

both studies were comparing homeopathic treatment to a placebo treatment. The results from the meta-analysis are shown in Figure 3-3. The standardised mean difference was used because although the outcome was the same, Rahlfs and Mössinger 1976 (Rahlfs and Mossinger 1976) measured the outcome on a three point scale and Rahlfs and Mössinger 1979 (Rahlfs and Mossinger 1979) measure it on a four point scale. Heterogeneity was not significant as measured by I^2< 50% and P of Chi^2 > 0.1. Therefore a fixed effect model was used. In Figure 3-3, Rahlfs et al 1976a is the comparison of asafoetida with placebo and Rahlfs et al 1976b is the comparison of asafoetida + nux vom with placebo.

Study	Outcome	Timing	Intervention 1 0.1% asa foetida			Intervention 2 0.1% asafoetida + 0.1% nux vomica			Control		
			Mean	Std dev**	N	Mean	Std dev	N	Mean	Std dev	N
Rahlfs and Mössinger 1976	Global improvement in IBS	8 days	0.62	0.59	21	0.47	0.51	19	0.43	0.51	23
		15 days	0.90	0.77	21	0.82	0.69	19	0.65	0.71	23
Rahlfs and Mössinger 1979	Global improvement in IBS	8 days	2.70	0.70	44				2.36	0.61	45
		15 days	3.11	0.83	42				2.49	0.77	43

Table 3-12: Results

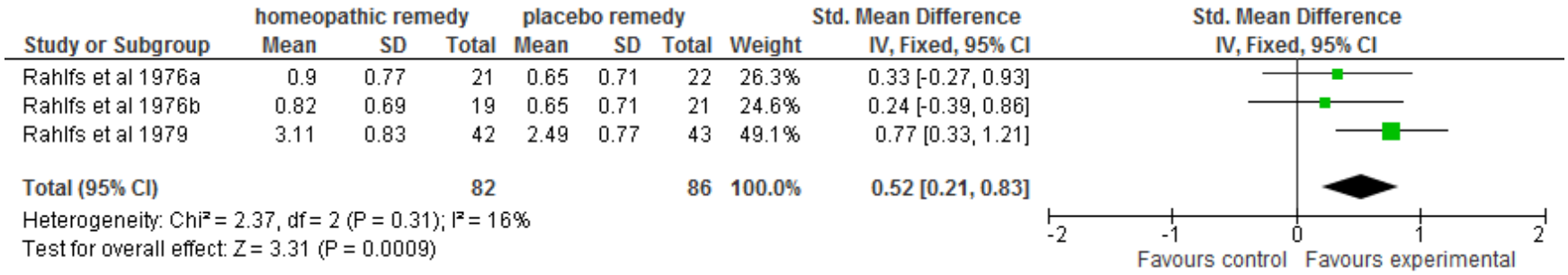

Figure 3-3: Results from a meta-analysis of included studies

The results from the meta-analysis show that homeopathic treatment using specified homeopathic remedies was more effective than placebo. However, this result must be interpreted with caution. This is because the quality of reporting in the including studies meant that it is difficult to assess whether or not these studies were carried out in a rigorous manner, and therefore how likely these results are to be a true reflection of the treatment effect. This, coupled with the fact that both the included studies assessed the effectiveness of pre-defined homeopathic remedies for IBS i.e. clinical homeopathy, suggests that more research is needed i.e. a study exploring the effectiveness of individualised homeopathic treatment would be useful.

This chapter has reported on a systematic review of the effectiveness of homeopathic treatment for IBS, and concluded that a trial evaluating the effectiveness of individualised homeopathic treatment for IBS would be useful. However the design of such a trial is not simple, the next chapter explains why this is so, and discusses what can be learnt from the methodological literature regarding trials of homeopathic treatment.

4 Trials of individualised homeopathic treatment

The previous chapter concluded that a trial of individualised homeopathic treatment (IHT) for IBS was needed, however in order to design such a trial, the issues involved in designing randomised controlled trials (RCT) for complex interventions such as CAM treatments need to be explored. This chapter therefore sets out to do this before moving on to assess the strengths and weaknesses of previous trials exploring IHT. These previous trials were studied to assess whether any of the designs would provide an appropriate means of assessing the effectiveness of homeopathic treatment for IBS. On studying these designs it became apparent that to define a control for IHT (in the context a clinical trial), was not simple and that an alternative approach was needed.

4.1 The suitability of randomised controlled trials for CAM

Randomised controlled trials are considered to be the gold standard of evidence when assessing the effectiveness of an intervention (Akobeng 2005). This is because the randomisation process seeks to prevent any systematic differences between the arms of the trial (Torgerson and Torgerson 2008). The lack of systematic differences aims to minimise a number of potential biases and create a situation whereby any differences in outcome are due to differences between the comparator interventions, rather than due to existing differences between the groups. RCTs can take two different approaches; explanatory or pragmatic (Schwartz and Lellouch 2009). Explanatory trials are used to determine whether or not a treatment has any efficacy in an ideal experimental setting. They usually compare the experimental intervention with a placebo. Pragmatic trials seek to explore the effectiveness of an intervention as it would be applied in practice. Consequently, the results of pragmatic trials are more generalisable than the results of explanatory trials (MacPherson 2004).

Despite the strengths of the RCT, its applicability for testing CAM has been questioned due to its reductionist nature, which results in a difference between how a CAM therapy is applied in a RCT and how the treatment would be delivered in everyday practice (Barry 2006). One of the issues in designing a CAM RCT is the difficulty in terming what the active ingredient in CAM is. This is because the therapeutic effect is often not solely confined to the acupuncture needles or the homeopathic remedy, but is an intertwined

process between the needling or remedy, the patient, the practitioner, and the diagnostic process (Carter 2003). In IHT the prescription of a homeopathic remedy requires an in-depth understanding of the patient and their illness, which cannot be achieved though the use of a formulaic process. Although any treatment can be holistic provided it is applied in a holistic manner, the theory underpinning many CAM treatments is that of viewing the body as a whole system. Therefore CAM treatments are often complex and multi-stranded. This leads to a difficulty in designing a RCT that adequately represents how the treatment is delivered in practice, due to the differing philosophical beliefs about health and disease in CAM. This is not unique to CAM and homeopathy, but can be the case with other complex interventions.

In terms of homeopathic philosophy, symptoms are seen as a manifestation of a single disturbance rather than a group of unrelated symptoms caused by different disorders (Vithoulkas 1998). Thus although in conventional terms a person may have been given multiple diagnoses, in the practice of IHT those same symptoms would all be viewed as part of one single disturbance. The aim of IHT is to prescribe a single remedy to relieve all the symptoms of that single disturbance. Within the philosophy of IHT, as described by Hanhemann, symptoms are a manifestation of a disturbance within the “vital force” and as such cannot be separated into multiple diagnoses. This is one of the fundamental tenets of IHT (Hahnemann, 1996). Therefore a well-selected homeopathic remedy should lead to improvement in that single disturbance, and a reduction in all symptoms. When a remedy acts in this manner it is referred to as that person’s “constitutional” remedy. Whilst it is possible that some IHT practitioners prescribe more than one remedy at a time, this is due to uncertainty over which of a particular group of remedies to prescribe, or as an adjunct to the “constitutional” remedy to enhance its effectiveness. However the aim of IHT practitioners is to determine a single constitutional remedy through a detailed case taking. This differs from the conventional model whereby a person may be offered different treatments for each of the different conditions. This also leads to a difference in the understanding of symptoms, with homeopaths viewing the appearance and disappearance of symptoms in a different manner to that of conventional medicine. For example one of the indications of a well selected remedy is the return of old symptoms (symptoms a person has suffered with in the past). The return and subsequent disappearance of old symptoms is seen as indicative of a patient being restored to health (Vithoulkas 1998). Thus the prescription of homeopathic remedies requires a detailed

understand of the patient's symptoms, any interruption to this understanding can lead to confusion and difficulty in knowing how to proceed with treatment. This can occur in trials where the homeopath is blinded to whether the patient has received placebo or not, as they are uncertain whether a lack of reaction is due to an ineffective remedy being chosen or due to placebo (Weatherley-Jones, Thompson and Thomas 2004), this is examined in more detail in Section 4.2.

It is the different understanding of illness and disease that sets CAM apart from conventional medicine. The assumptions of EBM and the biomedical approach require evidence of the efficacy of CAM for biomedically diagnosed disorders. However, CAM often has its own diagnosis procedures that influence how the treatment will be conducted (Barry 2006), with healthcare advice often being varied to take into account new problems that may arise during treatment, whether physical or mental/emotional (Paterson and Dieppe 2005). This means that trials that follow strict protocols as to how the treatment will be conducted do not replicate how CAM is delivered in practice. Yet these issues do not mean that it is impossible to carry out an RCT of a CAM therapy, merely that there are problems that must be considered when designing a trial for a CAM therapy.

The next section discusses some of the RCT designs that have been used to explore the effectiveness of homeopathy and discusses their strengths and weaknesses. An understanding of these previous trials was needed to determine whether or not they provided an appropriate design for assessing the effectiveness of IHT for IBS, and if not what kind of design would be appropriate. The strengths and weaknesses of explanatory and pragmatic trials for assessing homeopathic treatment is first explored, before moving on to assess the usefulness of factorial trials in assessing IHT.

4.2 Explanatory trials

A summary of RCT findings carried out by the British Homeopathic Association found that from 1950 to the end of 2010, 156 RCTs representing research in 75 medical conditions had been reported, 135 as full papers in peer reviewed journals (British Homeopathic Association 2010). These figures give an indication as to the number of studies and range of conditions in which the effectiveness of homeopathic treatment has been explored. The majority of homeopathy RCTs (n=120), are explanatory trials that have assessed the homeopathic remedy, rather than the whole package of IHT. This is done by comparing a homeopathic consultation, plus a

homeopathic remedy to a homeopathic consultation, plus a placebo remedy. Figure 4-1 shows a schematic diagram of the standard design for RCTs of homeopathic treatment.

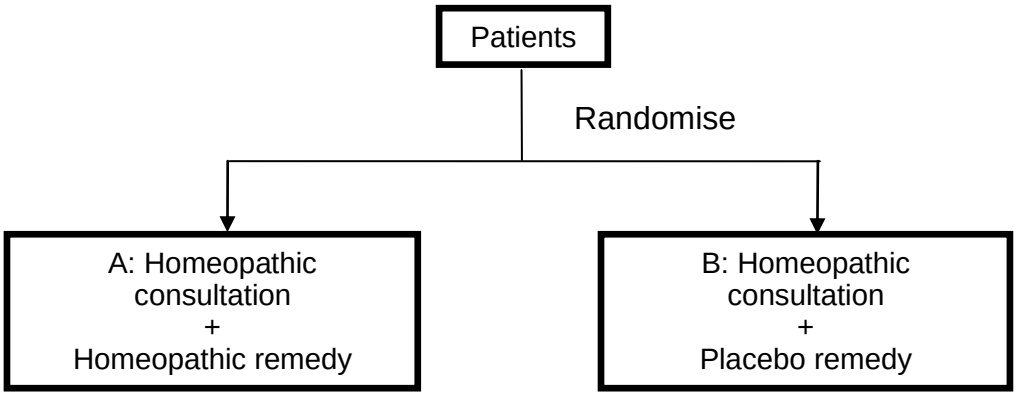

Figure 4-1: Standard design for RCT of homeopathic treatment

Trials comparing the homeopathic remedy (arm A) to a placebo (arm B) are exploring whether the homeopathic remedy has any efficacy and are not aiming to explore the effectiveness of the whole intervention of homeopathic treatment. In addition, they are unable to give information on the effectiveness of the homeopathic consultation, they can merely assess the efficacy of the homeopathic remedy. This type of trial has, in the past, been used to assess the effectiveness of IHT (Weatherley-Jones *et al.* 2004), clinical (Rahlfs and Mossinger 1979) and complex homeopathy (Jacobs *et al.* 2007). This type of trial is explanatory in nature and is designed to determine whether a treatment (in this case the homeopathic remedy), has any efficacy under ideal circumstances (Torgerson and Torgerson 2008). Explanatory trials have high internal validity as they control for known and unknown confounders through the intervention being precisely and rigidly described, and the use of tightly defined entry criteria. However care needs to be taken to ensure that the external validity of these trials is not compromised by the use of overly restrictive inclusion/exclusion criteria. This is because the use of strict criteria could lead to an unrepresentative sample that did not reflect the true population of the condition being studied and thus the results may not be generalisable.

The usefulness of studies that compare homeopathic consultation plus homeopathic remedy, to homeopathic consultation plus placebo remedy, for assessing IHT as a complex intervention (rather than the remedy), is questionable. This is primarily due to the complex nature of IHT and the

interaction between the homeopath and the patient. In a trial of IHT for chronic fatigue (Weatherley-Jones *et al.* 2004) the homeopaths taking part in the trial found it difficult to determine how to proceed after the first and subsequent consultations. This was due to an uncertainty about the placebo, as a patients reaction or lack of reaction to a remedy can be very important in deciding on the next prescription (Henriques 1998). This means that the patient's reaction to the homeopathic remedy can affect how the homeopath conducts the consultation. Therefore it is likely that the specific effects of the homeopathic remedy and the non-specific effects of the consultation are not independent of each other. The specific effects of the remedy are taken to be beneficial effects that would not be observed with placebo, whilst non-specific effects of the consultation are taken to be effects that would occur within any consultation with a caring practitioner. If the specific effects of the remedy, and the non-specific effects of the consultation are interrelated, then this means that it would be impossible to separate out the effects of the remedy and the effects of the consultation. This means that the effects of the remedy and the effects of the consultation cannot be separated and may be more than the sum of their parts. In addition, comparing a homeopathic consultation plus a homeopathic remedy to a homeopathic consultation plus a placebo remedy means that both arms get a homeopathic consultation. This design fails to take into account whether or not there is a positive effect inherent to the homeopathic consultation. It could be that a benefit has arisen because of some element that is specific to a homeopathic consultation that would not be found in other consultations i.e. a specific effect of the homeopathic consultation, such as the remedy matching process. In such a design this would remain unknown. It is important therefore when conducting a study of homeopathic treatment to decide what it is that is being studied; is it solely the homeopathic remedy or is it IHT as a package (the consultation plus the homeopathic remedy).

4.3 Pragmatic trials

It has been suggested that pragmatic trials provide a means of assessing CAM as it is delivered in practice (MacPherson 2004). A pragmatic trial is a trial that assesses the effectiveness of a therapy as it is delivered in practice and the therapy is usually compared to usual care or no treatment. Four pragmatic trials comparing IHT to usual care have been identified, although there may be others (Owen 1990; Fixsen, Vickers and Harrison 1999; Relton *et al.* 2009; Thompson *et al.* 2011). Figure 4-2 shows a schematic diagram

of a pragmatic trial design for a RCT of homeopathic treatment that is setting out to compare homeopathic treatment as a whole, single intervention, with an alternative system of care.

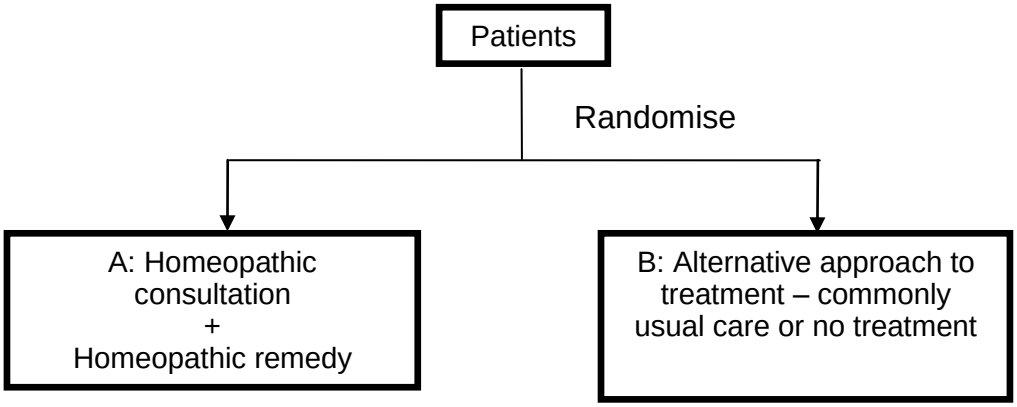

Figure 4-2: Pragmatic trial design for a RCT of homeopathic treatment

These trials aim to explore the effectiveness of homeopathic treatment as it is delivered in everyday practice. They compare the whole intervention of homeopathic treatment (arm A) with either no treatment or usual care (arm B), or sometimes another treatment. They can give information about the relative effectiveness of homeopathic treatment compared to no treatment/usual care or another treatment depending on what arm B comprises of. What they can't do is give information about exactly what components within the intervention have led to any effects, therefore when assessing homeopathic treatment pragmatic trials cannot be used to determine the effectiveness of the remedy alone. This fact has led them to be criticised for being bound to find a positive result (Ernst and Lee 2008; Perry, Terry and Ernst 2010). This is because one arm of the trial is getting time and attention that the other arm isn't getting, and it may be that this time and attention is leading to a benefit rather than an inherent effect of the treatment itself. Whilst it is true that a trial comparing homeopathic treatment to usual care cannot give information about whether or not homeopathic treatment is any better than spending time with an empathetic practitioner, this type of trial can give information on the clinical effectiveness of homeopathic treatment compared to usual care. In addition, a pragmatic trial comparing homeopathic treatment to usual care for glue ear did not find a positive result (Fixsen, 1999). However some critics of homeopathic treatment believe that in order to decide whether or not homeopathic treatment is effective, there needs to be proof as to whether the homeopathic remedy is efficacious (Ernst 2011), which pragmatic trials of

homeopathic treatment are not able to do. In addition, it is possible, in a pragmatic trial, where practitioners are able to practice as they would in everyday practice, that there will be some variability due to practitioners. In a real world setting IHT prescribers (classical homeopaths) may not all prescribe in exactly the same manner. It could be that some practitioners would adhere strictly to prescribing only one remedy at a time, whilst others prescribe more than one remedy, as described in Section 4.1. One of the strengths of pragmatic trials is that they allow practitioners to behave as they would in everyday practice and hence are often more generalisable than explanatory trials. In a pragmatic trial restricting their ability to prescribe as they would in everyday practice may lead to results that are less generalisable. It is inevitable that practitioner variation does exist. However to explore the impact of this variability a specifically designed study would be required.

4.4 Factorial trials

Another method that could be used to evaluate different elements of a complex intervention is a factorial study design. Factorial designs aim to take into account the entangled nature of multiple elements of an intervention such as IHT (consultation and remedy) and enable the researcher to determine the relative contribution of the different parts (Torgerson and Torgerson 2008). The simplest type of factorial design is a 2x2 factorial design as shown in Figure 4-3 for IHT.

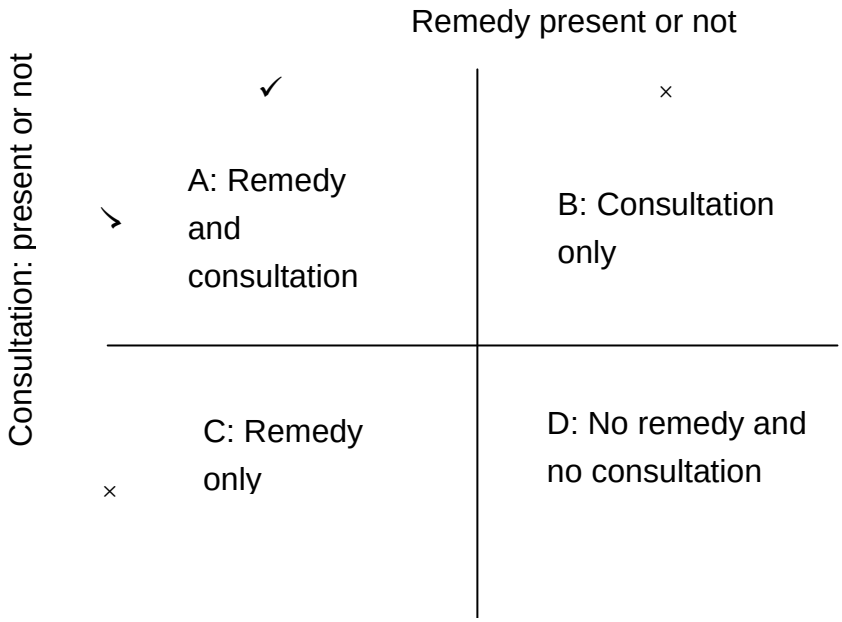

Figure 4-3: 2x2 Factorial design

This design aims to break IHT into component parts and in the subsequent statistical analysis determine the relative contributions of each component part, along with detecting whether there is any synergy between the component parts (Torgerson and Torgerson 2008). Whilst in theory this design could potentially provide a means of assessing IHT, in practice there are some concerns. Some of these concerns are generic to factorial designs and others to a factorial design for IHT. One of the issues of factorial designs is their complexity. This is especially the case in designs of a higher order than 2x2, where the recruitment process can be confusing for participants and researchers alike. In addition, there can be a problem with the powering of such trials. This occurs particularly if there is a negative interaction between two of the components (i.e. the sum of the two treatments is less than their individual contributions), thus giving rise to a decrease in the effect size. If this interaction was unknown prior to the study, then it could result in an inadequately powered trial due to the actual effect size being lower than anticipated. Furthermore a large sample size is required to fully power a factorial trial that is able to detect interactions (Torgerson and Torgerson 2008). Inevitably there will be an increase in cost associated with an increase in trial size.

In terms of factorial designs applicability to IHT, the main problem lies with how to construct the different arms. The no consultation and no remedy arm (marked D in Figure 4-3) can be constructed as a usual care arm and the consultation and remedy arm (marked A in Figure 4-3) as a IHT arm. The

other two arms are more problematic though. In terms of arm B, in practice a homeopath would not conduct a homeopathic consultation and then not give a remedy, unless the patient did not need a remedy because; a) they did not have any health problems or b) the homeopath felt that a previously given remedy was still working (Henriques 1998). A way round this would of course be to give a placebo remedy, but there are reasons why this is not desirable, such as the homeopath's difficulty in assessing patient's progress and therefore their ability to prescribe appropriate homeopathic remedies as already discussed in Section 4.1. In terms of the remedy only arm (marked C in Figure 4-3); it could be argued that it is impossible to deliver an individualised homeopathic remedy without a consultation as it is the consultation that provides the information needed to prescribe the most appropriate remedy. Yet there is the possibility of using internet based homeopathy, whereby the patient fills out a form on the internet which is mailed to the homeopath who then prescribes based on this. In this form of IHT there is a minimal interaction between the patient and the homeopath and this would provide a possible way of prescribing an individualised remedy without the consultation. However as this is a relatively recent development in homeopathic prescribing there are so far a very limited number of practitioners experienced in this approach. In addition there is still an interaction between the homeopath and the patient, although limited.

4.5 Recent developments in homeopathic trial methodology

In more recent years studies such as those by Brien (Brien, Lachance and Lewith 2004) and Steinsbekk (Steinsbekk *et al*. 2005a; Steinsbekk *et al*. 2005b; Steinsbekk *et al*. 2007) have attempted to explore the effects attributable to the homeopathic consultation and/or the homeopathic remedy. Brien outlined a test model for separating the effects of the homeopathic consultation from the effects of the remedy, using a rheumatoid arthritis complex given to one group of people after having a homeopathic consultation, and another group without a consultation (Brien, Lachance and Lewith 2004). Figure 4-4 shows a schematic diagram of this trial.

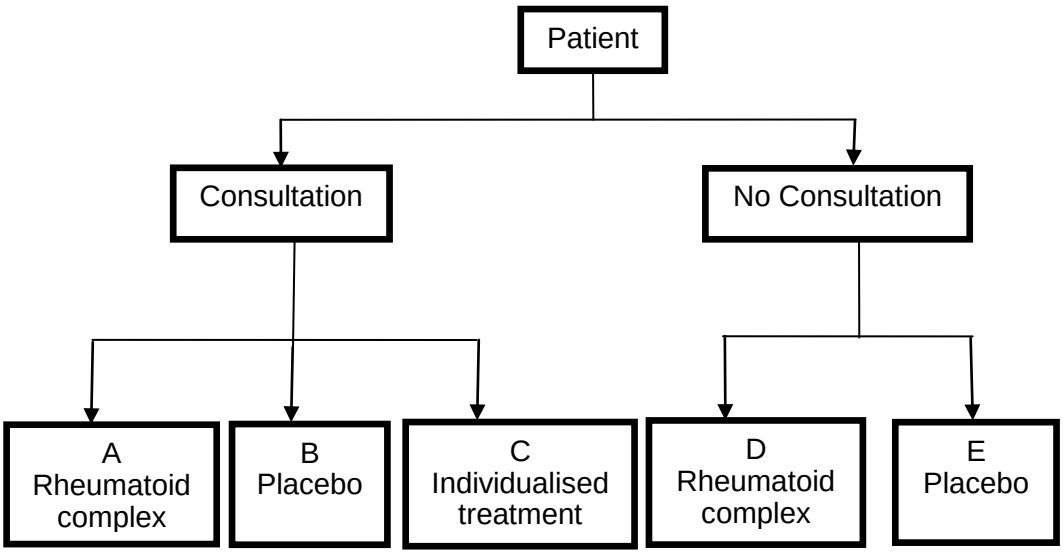

Figure 4-4: Schematic diagram of Brien's trial

Brien proposed making a number of comparisons.

To establish the effect of the homeopathic consultation by comparing;

- Arm A with arm D (homeopathic consultation + rheumatoid complex vs. rheumatoid complex).
- Arm B with arm E (homeopathic consultation + placebo remedy vs. placebo remedy).

To establish the effect of the individualised remedy by comparing;

- Arm C with arm B (homeopathic consultation + homeopathic remedy vs. homeopathic consultation + placebo remedy).

To establish the effect of the rheumatoid complex by comparing;

- Arm A with arm C (homeopathic consultation + rheumatoid complex vs. homeopathic consultation + placebo remedy).
- Arm D with arm E (rheumatoid complex vs. placebo).

To establish the difference between IHT and the rheumatoid complex by comparing;

- Arm C with arm A (homeopathic consultation + homeopathic remedy homeopathic consultation + rheumatoid complex).

Brien's trial therefore appears to be attempting to answer multiple questions (Brien, Lachance and Lewith 2004). The danger with trying to answer multiple questions is that it would require multiple comparisons. Without careful attention to how these multiple comparisons are adjusted for, it is highly likely that they will lead to a Type I error i.e. a difference is found

between the arms and a false null hypothesis is rejected in error (Benjamin and Hochberg 1995).

The ability of Brien's trial (Brien, Lachance and Lewith 2004) to answer these questions is debatable (Chatfield, Mathie and Fisher 2011). Trying to separate out the component parts of IHT into the consultation and the remedy, can be problematic in terms of constructing arms that adequately reflect IHT as it is delivered in practice (Weatherley-Jones, Thompson and Thomas 2004).

In terms of Brien's trial (Brien, Lachance and Lewith 2004) the question that the trial is most likely to be able to answer is, "is a homeopathic rheumatoid complex more effective than a placebo?" This comparison compares a homeopathic rheumatoid complex (with no consultation) to a placebo tablet. This comparison is more akin to the standard drugs trial, where the patient is receiving either a placebo or a genuine tablet. In this comparison nobody receives a homeopathic consultation and it is less likely that any additional effects will come into play.

In addition to the issues over what questions Brien's trial is able to answer, there is the question over multiple comparisons and adequate power. It was stated in Brien's protocol (Brien, Lachance and Lewith 2004) that 110 participants would be needed to detect a significant change in the primary outcome measure, however only 77 participants began treatment and only 56 completed treatment. This could have led to a lack of power to detect an effect, although the author claimed that post-hoc calculations revealed the study not to be underpowered. However post-hoc power calculations can be problematic and are not recommended (Hoenig and Heisey 2001). Furthermore, Brien proposed making six comparisons. Five outcome measures are mentioned in the protocol for Brien's trial, so if each comparison was made for each outcome measure, that would result in 30 comparisons. It highly likely that one of these comparisons would show a significant result due to chance, rather than there genuinely being an effect. This is a multiple testing effect and should be accounted for by methods that seek to reduce type 1 error – one of these is the use of the Bonferroni correction (Bland and Altman 1995).

In summary, this design is too complicated and tries to assess too many different complex variables at once. It is unlikely that this design will be able to give information on the effectiveness of IHT, as it is delivered in practice, or indeed the relative effectiveness of the homeopathic consultation or homeopathic remedy, as is claimed.

Steinsbekk (Steinsbekk *et al.* 2005a; Steinsbekk *et al*. 2005b; Steinsbekk *et al*. 2007) employed a different design to test the effect of the homeopathic consultation: homeopathic treatment was compared to self-prescribed medication in children. A schematic diagram of this trial is shown in Figure 4-5.

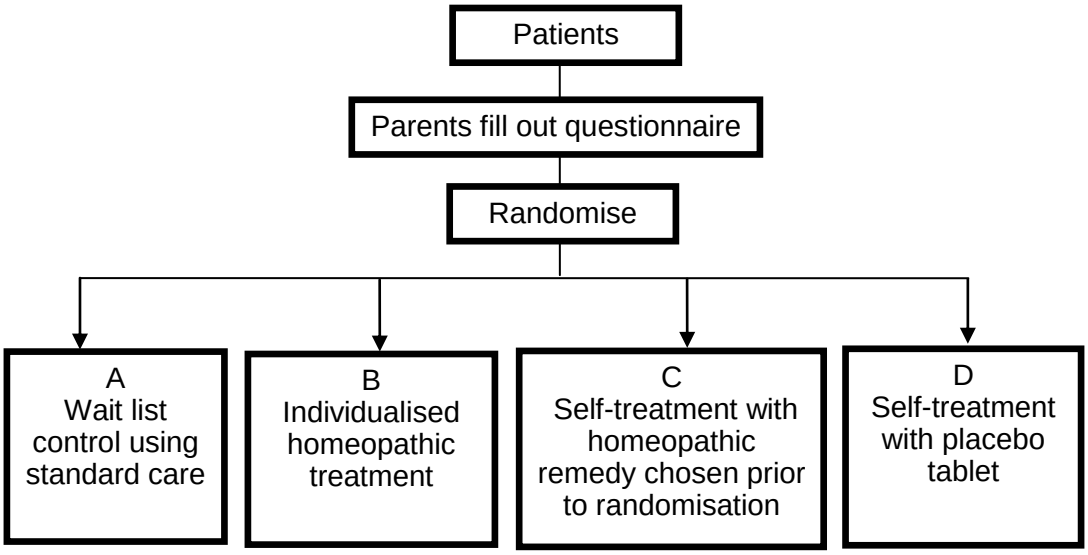

Figure 4-5: Schematic diagram of Steinsbekk's trial

This was a four armed trial which compared usual care (arm A) to preventative treatment (placebo or genuine) for an upper respiratory tract infection. In this study the children were recruited because they had visited a medical doctor for an upper respiratory tract infection (time frame of visit not clearly reported). Arm B involved the prescription of an individualised remedy after a homeopathic consultation. In arms C and D the parents filled out a questionnaire designed to identify the best of a choice of three remedies for the child, who was then subsequently given the remedy identified by the questionnaire (arm C) or a placebo tablet (arm D).

In this trial the comparisons made were:

- Arm A and arm B, i.e. standard care vs. IHT (Steinsbekk *et al.* 2005b)
- Arm B vs. arm C, IHT vs. self-prescribed remedy (Steinsbekk *et al.* 2007)
- Arm C vs. arm D self-prescribed vs. placebo (Steinsbekk *et al.* 2005a)

Each comparison in this study was reported separately.

Comparing arm B and arm C attempts to answer the question, “is IHT better than a self-prescribed remedy at preventing upper respiratory tract infections in children?” i.e. two different styles of homeopathic treatment are being

compared. This allows the relative effectiveness of homeopathic treatment compared to a self-prescribed remedy, when prescribed to children for the prevention of upper respiratory tract infection. The intention of this arm was to determine whether the homeopathic consultation has an effect. However, the difference between the two arms is not just the difference between having a consultation, or not, because those in the self-prescribed arm were given one of a choice of three remedies, whereas those in the consultation arm were given one of a choice of any of the remedies in the homeopathic pharmacopeia. Furthermore dosage instructions were different in the self-prescribed arm to the IHT arm. In the IHT arm the homeopaths varied the dosages according to the child, whereas in the self-prescribed arm all the children were given the same dosage. Therefore this comparison can give information about the two styles of homeopathy, but the reasons for any differences between the arms cannot solely be attributed to the consultation.

Comparing arm A and arm B attempts to answer the question, “is IHT for the prevention of upper respiratory tract infections more effective than usual care?” This comparison does not give any indication as to the efficacy of the different constituents of IHT but merely explores the effectiveness of the whole intervention IHT.

Comparing arm C versus arm D allows the effectiveness of a self-prescribed homeopathic remedy to be compared to a placebo treatment. These two arms were blinded, so that the child and their parents did not know whether the child was given the remedy they had chosen from the questionnaire or an identical placebo tablet. This comparison is thus designed to assess whether a self-prescribed homeopathic remedy is more effective than a placebo. However it cannot say whether a homeopathic remedy prescribed by a homeopath is more effective than a placebo.

Whilst there was no direct comparison between IHT and placebo, the authors extrapolated that, in the context of their trial, it did not matter whether patients used IHT, self-prescribed remedies or placebo (Steinsbekk *et al.* 2007). This conclusion is problematic as there was no direct comparison between IHT and placebo. Whilst the authors concluded that the effects of the consultation in their study is negligible (Steinsbekk *et al.* 2007), this may not be the case. This study was carried out in children, and in homeopathic consultations with children it is the parent/adult that does most of the talking. Thus it could be that any effects associated with the consultation are reduced for children. (Steinsbekk *et al.* 2007). This would be important if the consultation plays a significant part of any benefit associated

with IHT. In summary Steinsbekk's design has provided some interesting information, however it only gives information on homeopathic treatment for children, and it is likely that the experience of the homeopathic consultation will be different for adults.

A feasibility study trying to look at the specific and non-specific effects of IHT (Fisher *et al.* 2006) has been carried out to try and determine the relative contributions of each, the aim being to assess whether any benefits of IHT were due to something specific to IHT (a specific effect i.e. the homeopathic remedy), or due to something generic to many treatments that involve a consultation (non-specific effect i.e. the time and attention of a caring practitioner). A fuller discussion on the meanings of specific and non-specific effects and their relationship with the placebo debate was given in Chapter 2. In Fisher's trial patients were randomised to open label treatment or blinded treatment. A schematic diagram of this trial is shown in Figure 4-6.

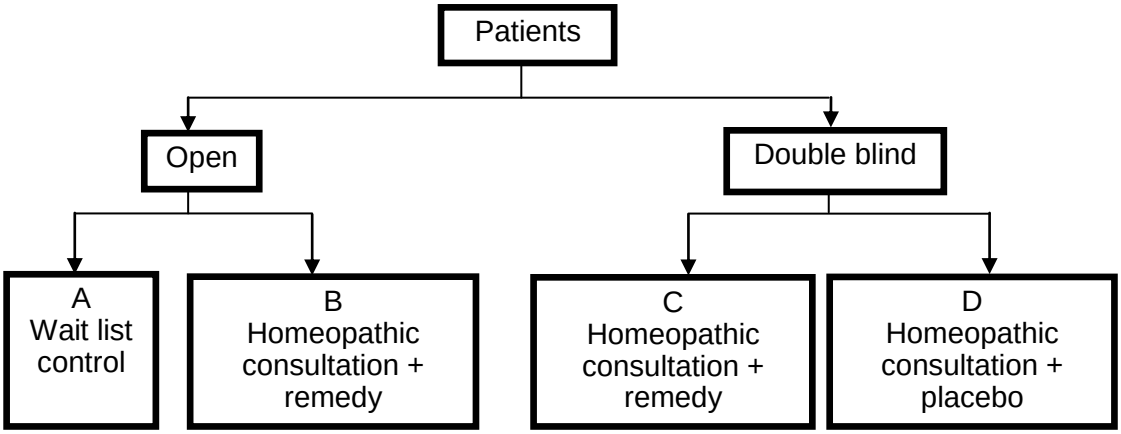

Figure 4-6: Schematic diagram of Fisher's trial

The open label treatments were IHT (arm B) or wait list control (arm A) whilst the blinded treatments were IHT (arm C) or homeopathic consultation plus placebo (arm D). Whilst the aim of this study was to elucidate the relative contributions of the specific and non-specific effects of IHT, unless it is assumed that the only effect specific to IHT is the homeopathic remedy, this trial design is not able to meet its aim because all arms are receiving a homeopathic consultation. By giving everybody a genuine homeopathic consultation it is not possible to assess the effect of any effects specific to the homeopathic consultation. It is likely that there are effects specific to the homeopathic consultation, as discussed in Chapter 2, a study of the specific effects of IHT identified two elements of the homeopathic consultation as being specific to a homeopathic consultation, the remedy matching process, and an in-depth enquiry into bodily complaints (Thompson and Weiss 2006).

Given this information, Fisher's study would not have been able to assess the relative contributions of the specific and non-specific effects of IHT. In addition, in his conclusions, Fisher concluded that this trial design was unlikely to be able to identify the relative contributions of specific and non-specific effects. This was because patients who were blinded to their treatment were more likely to drop out. In particular Fisher felt that blinded patients, who did not notice an improvement, were most likely to drop out, whilst patients who improved remained in the study, thus leading to an apparently positive effect of blinding. Unfortunately the reasons for dropouts were not reported, so although it is true that blinded patients were more likely to drop out, why this should have occurred can not be verified. It may be that Fisher's suspicion is correct; however without knowing the reasons for the dropouts this cannot be confirmed.

In summary, although Fisher's study provides an alternative trial designed assess the specific and non-specific aspects of IHT, the design is fatally flawed in that it would not have been able to do what it set out to do for the reasons described above. Furthermore, in reality, it was found to be unfeasible to conduct such a trial due to poor recruitment rates and differential drop out. The reasons for the poor recruitment rate are unclear, even in the worst case scenario of being randomised to the placebo remedy arm, the patients would still get a genuine remedy once the trial was completed. In addition, this would have been in the same time scale that they would have received genuine treatment had they not taken part in the trial, i.e. they had nothing to lose by consenting to be in the trial. This was pointed out to potential participants in the invitation letter, therefore the reasons behind patients reluctance to be in the trial is difficult to understand without interviewing the patients to find out why this was so.

Adler (Adler 2011) has proposed a novel study design, a schematic diagram of which is shown in Figure 4-7.

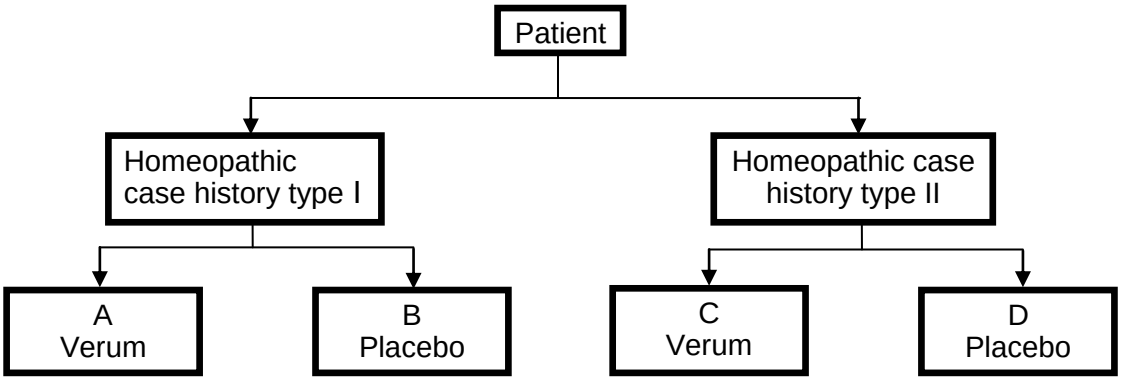

Figure 4-7: Schematic diagram of Adler's trial

This trial is designed to assess the efficacy of IHT in treating depression. In this placebo controlled 4-armed trial participants are randomised to homeopathic case taking type I with a genuine remedy (arm A), homeopathic case taking type I with placebo (arm B), homeopathic case taking type II with a genuine remedy (arm C), or homeopathic case taking type II with placebo (arm D). All the patients in the trial are blinded to the treatment they receive, whilst the homeopaths delivering the treatment know which case history type they are following. However the homeopaths do not know whether the patients they are treating are receiving a genuine or a placebo homeopathic remedy. This is potentially an interesting design. Unfortunately to ensure patient blinding exactly what homeopathic case taking type I and type II entail has so far not been published. This means that exactly what this study is trying to ascertain about case taking remains unclear without further information about the case taking methods. For example the study could be trying to assess the contribution of talking to an empathetic practitioner by comparing a supportive case taking method to a more formal and "cold" case taking, as was the case in Kaptchuk's acupuncture study (Kaptchuk *et al.* 2008). Or it could be contrasting two different schools of case taking, such as following a more traditional Hannemanian method to the newer Sankaran method[1].

[1] The Hanemanian method involves an in-depth enquiry into bodily complaints coupled with an exploration of the characteristics of the person, whilst the Sankaran method also know as the "sensation method" aims to uncover a persons "vital sensation" through a more abstract case taking. A full discussion of this method can be found in Sankaran's book "The Sensation." SANKARAN, R. 2004. *The Sensation in Homoeopathy.* India: Homoeopathic Medical Publishers.

4.6 Other studies of homeopathic treatment

This section explores some of the other types of studies that have been carried out to assess homeopathic treatment, beginning with a discussion on observational studies and why their results cannot necessarily be directly attributed to homeopathic treatment. It then moves on to discuss studies that have looked in more depth at the homeopathic consultation, and the kind of information that they have been able to give.

4.6.1 Observational studies

Observational studies are non-randomised studies where data is gathered on people exposed to an intervention; this data may or may not be compared to data from people who have not been exposed to that intervention (Torgerson and Torgerson 2008). Observational studies can also give information about the natural history of a disease in a "real-world" situation, and it is possible to observe large numbers of people over a long time scales. In observational studies, where there is a comparator group, there is a weaknesses due to the lack of randomisation. This means that it is not known whether or not any differences observed are due to the effect of the intervention, or due to an inherent difference between the two groups. Furthermore for observational studies in which there is no comparator group (i.e. the data on those who received the intervention is not compared to data from people who didn't receive it), it cannot be known whether any improvements observed are genuinely due to the treatment or to other factors such as regression to the mean. In the case of conditions such as IBS, it is likely that patients would consult the doctor when they were feeling at their worst and so were likely to improve (regress to the mean), whether they had treatment or not (Torgerson and Torgerson 2008).

One of the largest observational studies of homeopathic treatment is a 6 year study carried out by Bristol Homeopathic Hospital involving over 6 500 consecutive patients and over 23 000 outpatient consultations from 1997 to 2003 (Spence and Thompson 2005). This study aimed to assess the health changes of all patients who attended the hospital during this period. Patients were asked to rate the overall change in their health since their first visit, using the outcome scale shown in Table 4-1.

Outcome	Score
Much better	+3
Better	+2
Slightly better	+1
No change	0
Slightly worse	-1
Worse	-2
Much Worse	-3

Table 4-1: Outcomes used in Bristol study

The results found that following homeopathic treatment over 70% of patients reported some degree of improvement in their health and 50% reported a major improvement. However there is a potential for bias in that the outcome measure used was completed in the presence of the doctor and therefore the patients may not have been honest in their reporting, due to not wanting to disappoint the doctor, leading to a possible overestimation of the effect i.e. social desirability bias (Fisher 1993). It is also possible that there was a degree of recall bias in this study, where patients are more influenced by their current state than their previous state and find it difficult to remember how they were before, therefore comparisons to how they used to be may not be accurate (Schmier and Halpern 2004). Furthermore as there is no comparator group, it cannot be certain as to whether the patients would have improved to the same degree without treatment anyway. The large scale of the study and the fact that it reflected real-world circumstances are the strengths of the study.

Another long term prospective, multi-centre cohort study involving 103 homeopathic primary care practices (Witt *et al.* 2005) in Germany and Switzerland recorded data from all first time consulters (2,851 adults and 1,130 children) and had similar findings. In this study all patients who consented to take part and were consulting the participating homeopathic doctor for the first time were included, regardless of their diagnosis; 103 doctors took part in the study. The main outcome measures were patient and physician assessments and quality of life using the KITA questionnaire for children aged between 1 and 6 (completed by their parents), the KINDL questionnaire for children aged between 7 and 16 and the SF-36 for people aged over 16. These were completed at baseline and after 3, 12, and 24

months and returned to the study office in a sealed envelope, i.e. they were not completed in the presence of the doctor as was the case in Spence and Thompson's study (Spence and Thompson 2005). Completing a questionnaire in the presence of a doctor as already mentioned, may lead to the patients overestimating how much they had improved, in an attempt to avoid disappointing the doctor (Fisher 1993). Witt calculated the improvement that could be expected due to regression to the mean, using a previously established method (Hannan *et al.* 1994). Comparing the calculated value with the results of her study she found that the improvements found in her study were greater than would be expected to be attributed to regression to the mean (assuming the subjects in the study were no more ill than a random sample from the general population). These were maintained up to the 24 month follow-up. The study therefore concluded that it is probable that users of homeopathic treatment will improve considerably. However as the authors acknowledged, this improvement cannot be attributed solely to homeopathic treatment. The uncontrolled nature of this type of study means that participants may at the same time have been seeking other treatments or doing other things that could have led to, or contribute to, their improvements. A subsequent follow-up from Witt's study which was carried out after 8 years has also been reported (Witt *et al.* 2008). The improvements found in the previous study continued to be maintained up to eight years after inclusion into the study. Again this improvement may not be due solely to homeopathic treatment. Despite this Witt's study provides a good indication that people who seek homeopathic treatment will improve, however why they improve cannot be verified; whether it is due to a factor specific to homeopathic treatment, placebo effects, regression to the mean, withdrawal bias (where participants who do not perceive a benefit withdraw from the trial) or something else remains uncertain.

4.6.2 Studies looking at the homeopathic consultation

The homeopathic consultation is an integral part of IHT, and as such it is important to explore studies that have investigated the consultation, as these studies may shed light on factors to consider when designing a trial to assess the effectiveness of IHT, along with providing insights into how to design such a trial.

Various studies have been carried out to determine the different elements involved in the homeopathic consultation, in terms of both what the consultation is like and attempting to understand what the active ingredients

of a homeopathic consultation may be. This section provides an overview of some of the studies that have examined, what the homeopathic consultation is like, and explores what they have been able to say about homeopathic treatment and in particular the homeopathic consultation.

Eyles Eyles et al. 2010) looked into the homeopaths perception of the consultation which led to the formation of a model entitled, “a theoretical model of a UK classical homeopathic consultation”. This theoretical model identifies the different elements that play a part in the homeopathic consultation and how they are interrelated from the homeopaths perspective. The elements identified were; connecting, exploring the journey, finding the level, understanding self and responding therapeutically. The element “connecting” refers to the connection between the homeopath and the patients and covers areas such as empathy and rapport. “Exploring the journey” involves the patients disclosing information about themselves and their illness. The homeopath will then attempt to unravel this information, thus allowing them to gain an understanding of the patient. “Finding the level” involves evaluating the patient in terms of their illness, prognosis and most appropriate treatment. “Understanding self” refers to the need for the homeopath to understand themselves in order to be able to connect with the patients and provide effective treatment. Finally “responding therapeutically” refers to how the homeopath is able to respond to the patient’s needs and provide treatment fitting for the particular patient. Data from interviews with homeopaths, an examination of videos of homeopathic consultations and homeopaths diaries were triangulated. The model looks at the homeopathic consultation from a particular perspective of the homeopath, and therefore cannot tell us anything about how the patient views the homeopathic consultation. However the study states clearly that it is about homeopath’s perspectives, so although its generalisability to how the homeopathic consultation is viewed in the round could be questioned, its generalisability to the population studied is less questionable. Although a potential weakness of the study is the fact that no medical homeopaths were interviewed, it is unknown as to whether this group of homeopaths would have a different view of the homeopathic consultation and therefore how applicable the model would be to this group. However the final model was shown informally to medical homeopaths, (by Eyles), who agreed with its findings, therefore it is likely that medical homeopaths, to some degree, hold a similar view of the consultation to professional homeopaths. The fact that information was gathered from a variety of sources, interviews, videos and diaries gives added weight to the final model produced and is one of the

studies strengths. However only a limited number of homeopaths had agreed to be videoed and it may be that there are differences between how those who agreed to be videoed and those who didn't agree to be videoed, conduct a consultation. It is also possible that the presence of a video camera may have affected how the consultation was conducted. In summary, whilst it is considered likely that the model gives a good representation of the homeopathic consultation from a homeopath's perspective – which is what the study set out to do, it is also possible that patients would have a different view that would be worth exploring. Whilst this model doesn't focus on what effects are specific and what are non-specific to IHT, it does reveal the interconnectedness of the specific and non-specific aspects of IHT and proposes that these parts cannot be separated from each other.

Other studies have compared the homeopathic consultation to conventional consultations (Ruusuvuori 2005; Rise and Steinsbekk 2009). However these studies have not attempted to produce a framework or model of the constituents of the homeopathic consultation and so although they provide interesting comparisons, they have not tried to understand the constituents of the homeopathic consultation in terms of what is unique or not. For example Rise (Rise and Steinsbekk 2009) compared parents views of homeopathic consultations and conventional consultations and found that parents viewed homeopathic consultations to take a whole-person approach, whereas conventional medicine consultations were more symptom based. However what this "whole person" approach comprised was not elucidated (Rise and Steinsbekk 2009), and therefore what this study adds to the understanding of IHT and homeopathic consultations is questionable.

Brien (Brien, Leydon and Lewith In press) carried out a study which involved interviewing participants who had taken part in the RCT described in Section 4.5. The aim of the study was to explore rheumatoid arthritis (RA) patients' perceptions of the homeopathic consultation and whether they perceived any benefits from the consultation. From the interviews a model was constructed as to how the homeopathic consultation may help RA patients. The main themes of this model were; gaining advice from the homeopath, exploring their illness, exploring themselves and gaining emotional support. No mention is made of the homeopathic remedy within the model; this seems to be an oversight in that the ultimate aim of a homeopathic consultation is to facilitate the prescription of a remedy. Patients would have been aware of this and it seems likely that they would have mentioned the

remedy with regard to the consultation. Participants who had completed all five treatment sessions were interviewed. This could have led to a biased sample, as it is unlikely that those who did not perceive any benefit would attend all five appointments. The conclusion that patients experience a benefit from the homeopathic consultation cannot therefore be generalised to mean that all patients with RA will benefit from a consultation. The author states that 16 of the people contacted agreed to be interviewed, and that data saturation appeared to have been reached from these 16 interviews. It seems convenient that data saturation was reached within the number of people eligible and who consented to be interviewed. However, the resulting model is explained in depth, with examples of how the conclusions were reached. Thus, although there are concerns about some of the conduct of this study, it is likely that the model does reflect how those patients interviewed perceived the homeopathic consultation.

In summary these studies have provided some important information on what the homeopathic consultation is like.

4.7 Choosing an appropriate study design

The most important aspect of any research design is whether it is able to answer the question that is being asked. Thus when considering research designs the question should come first and the research design fitted to the question rather than the question fitted to the design, as is sometimes the case (Vickers et al., 1997). In this study the question posed is;

- Is IHT, as it is delivered in practice, any different to spending time with an empathetic practitioner?

In this chapter different designs of trials have been reviewed in terms of the information they are able to give about IHT. This PhD study aims to explore the effectiveness of IHT as it is delivered in practice. As already explained, pragmatic RCTs are able to explore treatments as they are delivered in practice (MacPherson 2004). However despite recent developments in IHT study design there have been no studies that have explored the whole package of IHT without trying to dismantle IHT into its component parts, or without comparing IHT to usual care. However comparing IHT to usual care is unable to answer the question posed in this PhD study as to whether IHT is any different to spending time with an empathetic practitioner. This is because the comparison of the IHT arm would get a consultation with an

empathetic practitioner, whilst the other would not. This leaves the question as to what to use as a comparator control for IHT.

In clinical trials one of the key issues to consider is what to use as a control. Part of the reason for the lack of studies exploring IHT as a whole package has been due to the difficulty in identifying a control that would provide equivalent time and attention to the homeopathic consultation, therefore controlling for any “consultational” effects. The next chapter explores how to design a control that would control for the time and attention involved in IHT.

5 Designing of a trial to assess the effectiveness of individualised homeopathic treatment

The purpose of this chapter is to determine how best to design a trial for individualised homeopathic treatment (IHT). In the previous chapter it was concluded that none of the designs that had been used in the past were able to determine whether or not IHT was any different to spending time with an empathetic practitioner. Thus a different approach was needed in designing such a trial. In the field of psychotherapy, due to the inherent difficulties in constructing a “control” arm for a treatment that involves a therapeutic interaction, researchers have spent time thinking about how to go about designing controls and what they should consist of.

One type of control used in psychotherapy research is an attention control (AC) or attention placebo. That is a non-specific treatment aimed at controlling for the time spent with an empathetic practitioner. In this PhD study the term “attention control” will be used, rather than the term attention placebo, to reflect the fact that this type of control is a non-specific rather than an inactive treatment. With this in mind this chapter discusses attention controls and important considerations involved in designing such a control, and in doing so draws on the conceptual issues explored in Chapter 2.

5.1 Attention control

Controls have been used in trials of behavioural therapies to test whether any positive effects of the therapy are due to; the generic aspect of spending time with an empathetic person or a specific aspect of the experimental treatment. These “time and attention” controls are often also known as “attention placebo” or “attention control” (AC).

ACs aim to give those in the control arm equivalent time and attention to that received by those in the active treatment arm(s).

The first published study (that was found), that talked about the use of an AC, was published in 1965 (Koenig and Masters 1965), and used “supportive counselling” as an AC in a smoking cessation trial using a behavioural therapy to aid cessation, signifying that this concept is not a new one and that all searches in this area should all go back to1965. In this study supportive counselling was used to control for the effects of talking to someone who showed concern and interest in the person, along with what

was felt to be the possibly beneficial effect of a figure they held in regard encouraging them to stop smoking. The supportive counselling involved discussing smoking and the reasons for smoking, encouragement when the person refrained from smoking but understanding if the person was unable to stop i.e. providing the person with a supportive environment in which to discuss their habit and ways of breaking it.

Before looking in more detail at ACs it was necessary to understand “what constitutes an “attention control?”” To this end a scoping search was carried out in Web of Science using the search term “attention placebo” (1898-2009). “Attention placebo” is the term more commonly used to describe these “time and attention” controls, however, the author prefers to use the term “attention control”, believing this term more accurately reflects the fact that these controls are not necessarily an inactive treatment. The aim was not to have a definitive search for all studies that had used an AC but rather to find a range of studies to compare and contrast and gain an idea of “what constitutes an AC.” At this stage the search was restricted to trials to gain a perspective on attention placebos that was not coloured by having previously read opinion or discussion pieces.

The search brought up 68 citations. Of these the “active” treatments involved a behavioural therapy, psychotherapeutic intervention, educational program, relaxation, exercise training or hypnosis. In order to better understand “what constitutes an “attention placebo?” it was desired to review in more detail a subsection of these 68 trials. To do this it was decided to choose one experimental treatment and extract data from all trials of that experimental treatment. The experimental treatment chosen was Cognitive Behavioural Therapy (CBT) because this was the experimental treatment most prevalent, with 9 of the available trials comparing Cognitive Behavioural Therapy (CBT) to AC. Data was extracted on: the condition treated, what the attention placebo comprised of, any rationale given for the AC, whether any checks were carried out to verify the integrity of the therapy delivery and whether or not it was the same person or group of people that delivered the CBT and the AC. Table 5-1 provides a summary of the results. The aim of this data extraction being to gain an understanding of some of the issues surrounding the choice of an AC, and ways in which these issues had been dealt with.

Article	Condition	Treatment 1	Treatment 2	Attention Placebo	Rationale for attention placebo	Details of attention placebo	Therapist	Check of integrity of therapies/ credibility check
Amigo 1991	Essential hypertension	Cognitive behavioural program		Regular contacts between therapists and patient	Control for regular interaction and relationship between subjects and examiners.	Discussed daily experiences with therapist encouraging patients to overcome stress without telling them how to.	Doesn't say	No
Thackwray 1993	Bulimia Nervosa	CBT	Behavioural therapy	Non-specific self monitoring	No specific rationale given.	Patient completed self-monitoring form and spent time with therapist, aiming to instil positive expectancies without giving specific advice.	Same	Yes - subjects completed check lists to check therapists covered certain subjects. Some sessions were audio taped and checked.
Heimberg 1998	Social phobia	Cognitive behavioural group therapy	phenelzine	Educational supportive group therapy	Use of appropriate control provides a stern test of the utility of the treatment.	Topics relevant to social phobia were presented and discussed.	Same group	Yes - Credibility of treatment checked.
Thomas 1999	Sickle cell disease (SCD) pain	Cognitive behavioural group therapy	No intervention	Discussion group chaired by a psychologist	Wanted plausible placebo that provoked similar expectancies to the treatment group.	Discussion of the type of problems and feelings associated with living with SCD.	Same	No clear information.
Lincoln 2003	Depression after stroke	CBT	Standard Care	Conversation with community psychiatric nurse	Results from previous studies may be due to having a supportive therapist to listen to problems.	Conversation with community psychiatric nurse focusing on day-to-day occurrences and physical effects of stroke and life changes.	Same	No
Thieme 2006	Fibromyalgia	Cognitive behavioural therapy	Operant behavioural therapy	General discussion	No specific rationale given.	Discussions centred on medical and psychosocial problems of Fibromyalgia.	Same team	No
Blanchard 2007	Irritable bowel syndrome	Cognitive behavioural group therapy	Intensive symptom monitoring	Psycho educational support groups	Commonly available treatment that would control for attention and group meetings.	Educational topics introduced by therapist and opportunity for members to share views and experiences.	Same group	Yes - doctoral student sat in on all groups as an observer.
O'Conner 2007	Delusional Disorder	Cognitive behavioural therapy		Individualised weekly meetings with one of the psychologists	Cognitive behavioural therapy has been found more effective when compared to routine care than when compared to an AC.	Individualised weekly meetings, involving non directive supportive discussion.	Same group	Yes - audio recorded and randomly selected for treatment integrity
Zautra 2008	Rheumatoid Arthritis	Cognitive behavioural therapy	Mindfulness meditation	Education only	Control for non-specific treatment effects such as attention, expectation and group support.	Information about rheumatoid arthritis and other health related topics given in a group setting.	Same team	Yes –audio recorded and listened to by treatment supervisor.

Table 5-1: Data extraction from nine trials that included an attention control

A variety of different ACs were used in these trials, all intending to control for the therapists' time and attention. However despite differences in the way they were presented, all of the ACs involved some kind of discussion about the problems associated with the patient's condition, either in a one-to-one format or in a group setting, depending on whether or not the trial was looking at group CBT. In all the trials it was the same person or group of people that delivered both the "genuine" therapy and the AC therapy. In five of the trials there was a check to confirm that in the AC arm an AC was being delivered rather than CBT. This data extraction provided a basis for further exploration of the notion of AC.

Thus to further this understanding a search was carried out in Web of Science from 1965 to 2010, using the search terms "attention placebo" OR "attention control". This was to identify articles explaining how and why particular ACs had been used to control against active interventions, the aim being to gain an understanding of the considerations that need to be made when considering what would be a suitable AC for IHT.

This search identified 880 papers, the abstracts of which were scanned to determine if the paper involved a study that had used an AC or was a discussion piece on ACs, the references of relevant papers were also screened in an attempt to locate any additional relevant papers. From this literature it was found, as in the previous search, that a variety of different ACs were used. However, on inspection, despite the different name tags given to the ACs many of them appeared to be essentially the same treatment, involving a non-directive discussion, often referred to as supportive listening/therapy (Whorwell, Prior and Faragher 1984; Guthrie *et al.* 1993), although the terms non-directive counselling (Ward *et al.* 2000) and brief non directive psychotherapy (Friedli *et al.* 1997) have also been used to describe what appear to be very similar treatments. These treatments, which will be termed "supportive listening" for the purpose of this thesis, all involve a non-specific treatment whose aim was to develop a supportive relationship by providing emotional support based on rapport and unconditional regard (Tarrier *et al.* 1998). However supportive listening does not involve some of the more advanced Rogerian counselling skills, such as problem clarification. It should be borne in mind that non-specific is not the same as inactive, the term "non-specific" is used to mean that the elements this treatment consists of are generic rather than unique. Supportive listening is considered to be a therapy in its own right and is used by

organisations such as Macmillan as a means of providing support to people in difficult situations (University Hospital of North Staffordshire NHS Trust 2012).

Others ACs involved relaxation (Boyce *et al.* 2003), support groups (Blanchard *et al.* 2007) or one-to-one education and discussion (Drossman *et al.* 2003). One thing all these AC interventions had in common was that they were all “off the shelf” interventions i.e. they were treatments that had already been used previously although not necessarily as an AC. For example relaxation therapy has been used in trials as an active intervention in its own right (Yu, Lee and Woo 2010). Whilst disease-specific support groups, both internet based and face-to-face, are a readily encountered and popular phenomenon.

Yet there were also trials found that had not used an “off the shelf” treatment, rather they had gone to considerable time and effort to design an AC specific to the treatment under investigation. The intention being to construct an AC that would be equivalent to the experimental intervention, with the therapeutically active factor(s) available only in the intervention group (Safer and Hugo 2006). This suggests that the AC should contain none of elements unique to the experimental treatment, whilst possessing the essential but non-unique elements to the same degree as the experimental treatment.

Thus it became apparent that when using an AC there is a basic choice to be made; either to use an already established non-specific treatment or to design an AC specific to the treatment under investigation. However, when attempting to design a new and credible AC, there is always the possibility of creating an intervention that is effective in its own right. In one irritable bowel syndrome trial the author felt that failure to find a significant difference between the AC and active treatment was due to the participants in the AC (pseudo meditation and EEG alpha suppression bio-feedback group) converting it into an active and effective treatment (Blanchard *et al.* 1992). Whilst with some ACs it is difficult to see how this could be the case, such as one that involved listening to audio book segments (Jacobson *et al.* 2011), with other multifaceted ACs, such as the one described by Blanchard, it is possible that the different facets could interact, leading to an effective therapy. However it is also possible that this is wishful thinking on the part of the researcher when finding their “active” therapy to be no more effective than an AC. Using an AC that has already been used a number of times in

the past and whose effects are better understood would eliminate or reduce such concerns.

5.2 Structural equivalence

In addition to the thoughts about the contents of ideal comparison controls in respect to the specific and non-specific effects of the treatment being evaluated, the concept of structural equivalence has also been suggested as being important in preventing the introduction of bias (Baskin *et al.* 2003). Structural equivalence (Baskin *et al.* 2003) means that the structural aspects of the both the trial and control treatment are the same; all groups get the same number of sessions, with the same duration and over the same time frame. If any medication is given out then all groups would be given a medication, whether it be placebo or genuine. If tasks are given to do at home then all arms get tasks etc. Providing structural equivalence is important because any effectiveness observed in a trial where the arms are structurally non-equivalent may be down to the non-equivalence rather than any active effects of the treatment being assessed. For example, in a review of psychotherapy trials (Baskin *et al.* 2003) it was found that those where the control was structurally in-equivalent to the active treatment, there was a greater effect size compared to those that were structurally equivalent (i.e. same number of sessions, time spent with patient etc).

Finally, the view that the AC should be a credible treatment option for the condition in question should also be explored. Borkovec and Nau (Borkovec and Nau 1972) have developed a questionnaire to assess how credible people perceive the treatment they are receiving/are going to receive will be for their condition. This questionnaire has been utilised in trials using an AC. Credibility is important for two reasons: (i) the credibility of a treatment has the potential to provide a powerful therapeutic effect (Wampold 2001), (ii) there is likely to be an increased dropout rate in the AC arm if people think it is not going to be of any benefit to them.

Therefore from this review it can be summarised that an AC should:

- Be a plausible treatment for the condition being treated
- Not have a significant impact on the mechanism thought to explain the effectiveness of the investigational treatment.

- Be equivalent to the active treatment in terms of time spent with the patient.

5.3 Attention controls in irritable bowel syndrome trials

As already mentioned, one of the most important aspects when choosing an AC is that it is a credible treatment for the condition being treated (Whitehead 2004). Different ACs may appear credible for different illnesses. An AC that may be credible to a person with IBS may not be credible to a person with chronic fatigue; therefore it was felt that it was important to think carefully about the kinds of treatment that a person with IBS would believe may work. To this end a search was carried out to identify randomised controlled trials of IBS that used an AC. This was to allow exploration of the types of ACs used and their credibility to patients, with the aim of narrowing down suitable options for an AC in an IBS trial of IHT. The search was carried out in February 2010 and repeated in 2012, with the purpose of ensuring that up to date results were included in this thesis.

The search was carried out in Embase (1947 – June 20 2012), MEDLINE (1950 – June week 2 2012) and PsychINFO (1806- June week 2 2012) and Web of Science (from 1965 to week 22 2012) using the search terms “attention placebo”, “attention control”, “supportive listening”, “supportive counselling”, “supportive therapy”, “relaxation”, “non-directive counselling”, “brief psychotherapy”, “irritable bowel syndrome”, “irritable bowel disease”, “irritable colon” and the Mesh term “irritable bowel syndrome.” Full details are given in Appendix 3. Systematic reviews identified in the search were used to identify any further papers that may also have included an AC. A further search was also carried out in Web of Science (from 1965 to week 22 2012) to identify all the papers relating to IBS written by Whorwell or Blanchard, two researchers who are known to have used AC in IBS. A summary of the findings are shown in Table 5-2.

Reference	Experimental treatment	Attention control/comparator	Same contact time	Comments
(Whorwell, Prior and Faragher 1984)	Hypnotherapy	Psychotherapy and placebo	Yes	
(Blanchard *et al.* 1992) study 1*	Multi component (relaxation, thermal biofeedback and cognitive therapy) treatment	Pseudo meditation and EEG alpha suppression biofeedback	Yes	Credibility and expectations assessed by questionnaire
(Blanchard *et al.* 1992) study 2*	As above	As above	Yes	Credibility and expectations assessed by questionnaire
(Guthrie *et al.* 1993)	Psychotherapy	Supportive listening	No	
(Payne and Blanchard 1995)	Individualised cognitive treatment.	Self-help support group.	Yes	
(Fernandez *et al.* 1998)	As above	Visualisation of bowel function	Yes	High dropout rate in attention control arm
(Boyce *et al.* 2003)	Cognitive behavioural therapy	Relaxation therapy	No	
(Drossman *et al.* 2003)	Cognitive behavioural therapy	Educational support	Yes	Credibility and expectations assessed by questionnaire
(Simren *et al.* 2004)	Hypnotherapy	Supportive therapy, including dietary advice, telephone support and discussion with a consultant	No	
(Fernandez and Amigo 2006)	Training in stress management or contingency management	Biofeedback control	Yes	
(Blanchard *et al.* 2007)	Group based CBT	Psycho educational support groups.	Yes	
(Vlieger *et al.* 2007)	Hypnotherapy	Supportive therapy discussing symptoms and triggers.	No	
(Gaylord *et al.* 2009)	Mindfulness	IBS support group	Yes	Credibility assessed by questionnaires. Adherence to protocol assessed by video
(Craske *et al.* 2011)	Cognitive behavioural treatment targeting visceral anxiety.	Educational support	Yes	Credibility assessed by questionnaires. Adherence to protocol assessed by audio recordings
(Flik *et al.* 2012)	Individualised hypnotherapy	Group educational supportive therapy	Yes	
(Lindfors *et al.* 2012)	Hypnotherapy	Supportive therapy as per Simren's study	No	

Table 5-2: Attention controls used in IBS trials

The ACs identified in this search comprised: supportive therapy, psychotherapy + placebo tablet, psycho-educational support group, self-help support group, pseudo-meditation and EEG alpha-suppression biofeedback, education, biofeedback and visualisation. The controls used were not designed to be inactive treatments, rather they were designed to control for the non-specific effects of the experimental treatment. It should also be borne in mind that what is considered a non-specific treatment by some is considered to be an active treatment by others. In this PhD study a control treatment is taken to be a treatment that contains only generic elements and no elements that are not found in other treatments.

Of the list of controls identified in the searches, only supportive therapy/listening, pseudo meditation and self-help support groups were used as a control in more than one trial (Blanchard *et al.* 1992; Guthrie *et al.* 1993; Payne and Blanchard 1995; Simren *et al.* 2004; Gaylord *et al.* 2009). However the supportive therapy was not the same in all trials. In one of the trials it comprised a one-to-one supportive conversation (Guthrie *et al.* 1993), and in the other it comprised one-to-one discussions with four specialists in different areas, i.e. dietician, gastroenterologist etc. (Simren *et al.* 2004). Although relaxation therapy is shown in Table 5-2 as an attention placebo, in this trial there was a comparison of CBT and relaxation to test the hypothesis that CBT would be better than relaxation therapy. Furthermore, relaxation therapy for IBS appears to be a treatment in its own right and has been used as one of the active treatment options in two trials (Fernandez *et al.* 1998; Fernandez and Amigo 2006), see Table 5-2.

From the ACs identified as having been previously used in IBS trials the following were considered as potentially suitable as an AC for IHT; relaxation therapy, supportive listening, an education program, support group or designing an AC specifically for IHT. Designing an AC specifically for IHT was decided against because it was felt that it would not be feasible in the time scale of this project to design, test for credibility and then run a RCT with a specifically designed AC. ACs that had been specifically designed to contain the non-specific effects of a particular treatment, such as EEG alpha suppression biofeedback, were not considered because they had elements that were not a part of IHT, such as carrying out physical treatment. To aid in the decision as to what would be the most suitable AC for IHT a table (Table 5-3) of the specific and non-specific effects of IHT was constructed from

Thomson's work, that was discussed in Chapter 2 (Thompson and Weiss 2006).

Specific effects of homeopathic treatment	Non-specific effects of homeopathic treatment
• In depth enquiry into bodily complaints and idiopathic symptoms • homeopathic remedy • Remedy matching process	• Consultational empathy • Openness to mind body connection • Disclosure

Table 5-3: Specific and non-specific effects of IHT

Using Table 5-3 as a framework for identifying the non-specific aspects of IHT and considering the ACs chosen as being potentially suitable as an AC for IHT (relaxation therapy, supportive listening, an education program, support group), it was decided that an AC for IHT must contain a one-to-one interaction with an empathetic practitioner. This was because a one-to-one interaction would allow for the opportunity for disclosure along with providing consultational empathy. The opportunity for disclosure is important for IBS patients because, although IBS is perceived to be a physical condition, people with IBS are more likely to suffer with anxiety or depression than those in the general population (Ten Berg *et al.* 2006). Along with this is the fact that IBS is a condition that people often don't talk about. This is because of embarrassment and feelings of stigma due to a lack of understanding by friends and family about the effects of IBS (Silk 2001; Drossman *et al.* 2009). In a focus group study carried out by Drossman one participant said (Drossman *et al.* 2009) page 1538 "*I didn't tell my husband, don't tell my friends. I feel lots better now that I can talk about it."* This quote highlights the importance of being able to talk about IBS to IBS suffers.

Although a support group is an attractive option and appears in the literature to have been credible it is was not chosen because it is not a one-to-one interaction. It was felt that the AC must be a one-to-one interaction to allow for the possibility for disclosure and consultational empathy.

Despite relaxation therapy having been compared to cognitive behavioural therapy in an IBS study (Boyce *et al.* 2003) it was not chosen, because there is the potential that it could contain specific effects in its own right. Relaxation therapy comprises particular techniques aimed at releasing tensions in the body and promoting positive thinking, thereby helping the

person to cope in a stressful situation (Yu, Lee and Woo 2010). It has been shown to have physiological effects such as lowering the heart rate (Peveler and Johnston 1986), and for the purpose of this study is therefore considered to be an active treatment rather than a non-specific treatment. Another possibility was an education program as described in a cognitive behavioural therapy (CBT) trial (Drossman *et al.* 2003), whereby the participant reads a variety of educational materials and discusses them with the therapist. This appears to have been a credible therapy, is relatively easy to deliver and offers a one to one interaction. However the educational material may lead to some effectiveness of this intervention over and above spending time with an empathetic practitioner. It was therefore decided that supportive listening would provide the best AC for a trial of IHT because the non-specific aspects of IHT of consultation empathy and the opportunity for disclosure would be provided, without the specific elements of in depth inquiry into bodily symptoms, the remedy and remedy matching process. It was felt that although education could involve the same length of time spent with a practitioner, education doesn't perhaps have the same opportunities for disclosure as does supportive listening and IHT. In addition education could also include specific effects that IHT doesn't, thus introducing more variables.

As already stated supportive listening has previously been used as an AC in IBS trials and is therefore thought to be a credible treatment option. Consequently supportive listening is considered to be the most appropriate AC to control for therapists' time and attention in a trial of IHT because it is a non-specific therapy which can be used to give the same amount of time and attention to that received in a homeopathic consultation. Furthermore it has been used successfully in the past as a control in trials for IBS (Whorwell, Prior and Faragher 1984; Guthrie *et al.* 1993). In spite of this Whitehead (Whitehead 2004) advises on assessing whether a treatment is plausible by assessing the expectation of benefit through a treatment credibility questionnaire, and monitoring differential dropout rates. Should differential dropout occur the researcher can then seek to explore why this is so; is it because one treatment was less effective than the other, was it less acceptable to patients, or did patients not believe it would help them.

In summary supportive listening was believed to be the most appropriate treatment to control for the time and attention given to patients in a homeopathic consultation. However IHT involves the prescription of a

homeopathic remedy and therefore the issue of structural equivalence needs to be considered. This will be discussed in the next section.

5.3.1 Structural equivalence and the inclusion of a placebo tablet

As already mentioned structural equivalence is an important aspect of ACs, and when thinking about structural equivalence in terms of IHT, the homeopathic remedy must be taken into account. As already discussed in section 5.2, to provide maximum structural equivalence, if one group receives a medication then all groups should receive a medication.

In the searches for ACs, an RCT studying non-cardiac chest pain (Jones *et al.* 2006) was identified that compared hypnotherapy to supportive listening plus a placebo tablet. The authors justified the inclusion of the placebo tablet as being to boost any placebo effects in the supportive listening arm. The inclusion of a placebo tablet in a trial of IHT could be used to provide structural equivalence between IHT (where the patient receives a homeopathic remedy), and supportive listening. In this case both groups would receive time and attention from the therapist plus a medication, be it placebo or otherwise. The tablet used for the placebo could be sac-lac, the base tablet for a homeopathic remedy (consisting of lactose plus a binder); therefore the tablet would appear the same as a homeopathic remedy. However what and what not to tell participants about a placebo tablet poses an ethical dilemma. The effectiveness of the action of the placebo tablet ultimately rests on what patients are told about, as patients' beliefs will help to determine whether it has an effect. However what patients are told will have an ethical dimension. This will be discussed in Chapter 6, which focuses on the methodology of the study. The next section discusses the final element of an AC, that of who will provide the AC.

5.3.2 Who provides the attention control

Who would deliver the AC is another area that needs careful consideration. In the CBT trials shown in Table 5-1 the same group of people delivered the experimental and control treatments. A trial of IHT has the added complication that the homeopaths providing the IHT may not have had any formal training in supportive listening, whereas therapists trained in CBT are likely to have formal training in a wide range of counselling skills, including supportive listening. It is important that whoever delivers the AC is able to present it as a credible therapy and one aspect of this will be the confidence the person feels in delivering the therapy. The downsides of homeopaths

delivering the AC could be; inexperience and a vested interest in not allowing the supportive listening to appear credible thus introducing a bias into the trial. However using the same team of therapists to deliver both the interventions would lessen the variability due to therapist, but in reality homeopaths would never be asked to deliver supportive listening and thus this would not enhance the external validity of the trial. Weighing these things up, and with the thought that one of the most important aspects of an AC is that it appears credible, it would be better if a nurse or someone with basic counselling skills provided the supportive listening. When choosing such a person, care needs to be taken to ensure that both the homeopaths and the supportive listening provider have a fairly similar demeanour. There is the possibility of bias if one was a warm and empathetic person and the other(s) rather cold. In this scenario it would not be a test of the therapy but rather a comparison of different types of people.

This chapter has provided a discussion on the issues to consider when deciding on an AC for IHT. The chapter began with an investigation into how other researchers have constructed ACs, and the factors to consider when designing such a control before identifying a potential AC for IHT, namely supportive listening. However if IHT plus usual care was compared to supportive listening plus usual care it would not be known whether either of these treatments offered any benefit over usual care. This is important because it would be of no advantage to offer people a treatment that did not provide any additional benefit over their existing treatment.

Once a potential control (supportive listening) and a condition (IBS) had been identified, the next step was to decide on the methodology of the trial. The next chapter will therefore explain the reasons why the trial was conducted in the way it was.

6 Methodology

The conclusion from Chapter 3 was that a trial of IHT for IBS was needed. However as concluded in Chapter 4, the design of such a trial is not simple. Considering possible designs it was concluded in Chapter 5 that a trial comparing IHT plus usual care to both, supportive listening plus usual care, and usual care alone, was the most suitable design. In this design supportive listening would act as an attention control (AC), controlling for the time and attention the patient gets from the homeopath, and usual care would act as a baseline comparator. Thus it would be possible to assess not only whether IHT plus usual care was any different to supportive listening, but also whether IHT was any different to usual care alone. If a usual care arm had not been added this would not have been known. No matter how IHT performed in relation to supportive listening, it is a waste of resources to offer people with IBS IHT on top of their usual care if this elicited the same results as would be achieved with usual care alone. This chapter builds on the conclusions about the most appropriate study design and describes why the cohort multiple RCT design (cmRCT) was chosen. This PhD study was part of a wider trial assessing the clinical and cost effectiveness of IHT, this chapter describes the relationship between this PhD study and the wider trial before moving on to explain decisions made about the inclusion of a placebo tablet in the supportive listening arm, along with the choice of outcome measures. In addition it explores the rationale for including a qualitative element to this study and explains the reasons why individual interviews with participants in the RCT were selected for the qualitative part of the study.

6.1 Randomised controlled trial of homeopathic treatment for irritable bowel syndrome

In designing an RCT of IHT it is important to consider what the trial is trying to answer. In the case of this PhD the aim was to:

- Determine whether IHT, as it is delivered in practice, is any different to spending time with an empathetic practitioner.

Chapter 4 discussed various trial designs and their appropriateness in assessing homeopathic treatment. The aim of this study was to carry out a

trial that was both rigorous (had low susceptibility to bias and high internal validity), and that would be true to how IHT is delivered in practice.

Therefore it was concluded at the end of Chapter 5 that a pragmatic design would be the most suitable. Pragmatic trials are designed to assess how effective an intervention is, as it is delivered in everyday practice (MacPherson 2004).

The next consideration was what to use as a comparator or control. Chapter 5 discussed the idea of ACs and how to design an AC for IHT. At the end of Chapter 5 it was concluded that supportive listening would provide a suitable AC for IHT. Therefore the eventual study design was that of a three armed pragmatic RCT comparing:

- Usual care
- IHT plus usual care
- Supportive listening plus usual care

A usual care arm was included in the trial to provide a baseline for comparison, thus it would be possible to assess whether IHT was the same as, better, or worse than usual care.

The trial reported in this thesis is part of a wider trial looking at the clinical and cost effectiveness of IHT compared to usual care, in the treatment of IBS. The wider trial is seeking to answer the question, “Is IHT a cost effective treatment for IBS?” A previous trial (Relton 2009) comparing IHT plus usual care to usual care alone for fibromyalgia was carried out by the same team who are conducting the wider trial. In Relton’s fibromyalgia trial a significant positive effect associated with IHT was found. In a subsequent systematic review of homeopathy for fibromyalgia (Perry 2010), it was suggested that Relton’s trial would have been more meaningful if the homeopathic package of care had been compared to a package of care that controlled for the non-specific effects of the therapeutic setting. This was because comparing IHT against usual care could have led to a positive outcome for IHT due to the extra attention those in the IHT arm received, rather than due to the homeopathic remedy. In addition to this, when the team from the wider trial met with Professor Whorwell, (a gastroenterologist and researcher) he suggested that a third arm should be included in the wider trial (Raw 2010). The team, knowing that my area of interest was, “a time and attention control for IHT,” asked me to design an AC arm to include

in their wider trial. Thus this study became part of a wider trial. Figure 6-1 shows the relationship between this study and the wider trial. For the statement of providence from the protocol for the wider trial Appendix 4.

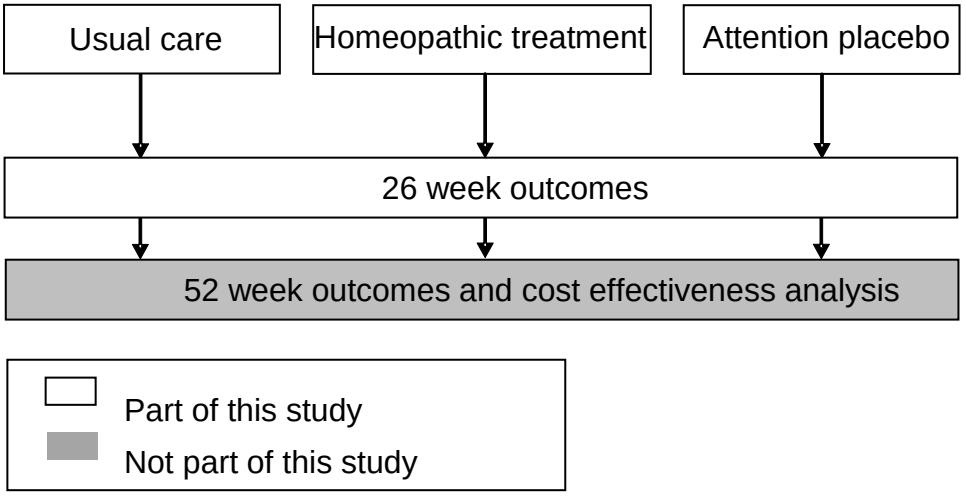

Figure 6-1: Relationship between this study and the wider trial

For the purpose of this piece of research the main area of interest is in the comparison of IHT to AC at 26 weeks, however to provide a baseline for comparison a usual care arm was also included. This will allow a distinction to be made between the “placebo” effect and the natural history of the condition. Thus if both the IHT and AC arms proved to be the same in terms of effectiveness (at 26 weeks) it was possible to address the supplementary question regarding whether there are any differences in outcomes for the active treatment arms compared to usual care.

The main area of interest to the wider trial is the clinical effectiveness and cost effectiveness outcomes of patients with IBS treated with IHT plus usual care, compared to those treated with usual care alone, 52 weeks after recruitment to the trial.

6.1.1 Setting and team

The trial took place at Barnsley Hospital NHS Foundation Trust, where both the IHT and the supportive listening were delivered. A consultant gastroenterologist and gastroenterology registrar formed part of the team for both this and the wider study. Two homeopaths who had previously been involved in a trial of IHT for fibromyalgia and who were already working at Barnsley Hospital provided the IHT.

6.1.2 Funding

The trial was funded by Barnsley Hospital small grants fund, Friends of Barnsley Hospital and the Homeopathy Research Institute. The Homeopathy Research Institute is a charity that is working to facilitate scientific research in the field of homeopathy. Potential sources of bias introduced by a homeopathic charity funding this trial and how they were addressed is discussed in Chapter 8. The trial was registered with the International Standard Randomised Controlled Trial Number Register (ISRCTNR), registration number: ISRCTN90651143.

6.1.3 Research question and hypotheses

Research Question

What is the difference between IHT and supportive listening for irritable bowel syndrome when compared against usual care?

Aim

To test whether IHT plus usual care is any different to:

- supportive listening plus usual care
- usual care alone.

Primary hypothesis

Ho: There is no difference between IHT and supportive listening when measured by change in IBS symptom severity score (IBS- SSS) between baseline and 26 weeks where IBS is defined by a score of ≥ 100 on the IBS-SSS.

H1: There is a difference between IHT and supportive listening for patients with IBS when measured by change in IBS-SSS between baseline and 26 weeks.

Secondary hypothesis

Ho: There is no difference between IHT and usual care when measured by change in IBS symptom severity score (IBS-SSS) between baseline and 26 weeks where IBS is defined by a score of ≥ 100 on the IBS-SSS.

H1: There is a difference between IHT and usual care for patients with IBS when measured by change in IBS-SSS between baseline and 26 weeks.

The primary hypothesis is looking at the explanatory question “is IHT functionally equivalent to time and attention?” The rationale for the primary hypothesis being the need to test the common assumption that IHT is nothing more than a placebo treatment and that IHT is equivalent to “supportive listening.”

As already explained the main area of interest in this thesis is whether or not IHT is any different to supportive listening, however to put these results into context, a comparison was made against usual care. Therefore the secondary hypothesis looked at the pragmatic question “is IHT more effective than usual care?” Thus a comparison was made as to whether IHT is any different to usual care.

The study used a Cohort Multiple RCT (cmRCT) design, the next section explains why this design was chosen rather than that of a standard RCT i.e. a two arm parallel group trial.

6.1.4 The cohort multiple RCT design

This trial used a cmRCT design (Relton *et al.* 2010). This is a recently developed design, similar to the Zelen design (Zelen 1979), where participants are randomly allocated to either the control or experimental group(s) prior to being told about and consenting to the experimental treatment. In the Zelen design consent is only sought from those allocated to the experimental treatment. Consent is not sought from those allocated to the control group and they are not told that they are involved in a comparative study. However in the cmRCT design a cohort of participants are invited to take part in an observational study entailing the completion of questionnaires at various time frames. Consent to “take part in an observational study” is sought from everybody who is invited to join the cohort. Those that do not consent do not form part of the cohort. This cohort is formed prior to the randomisation process and from the cohort people can be randomly selected to the “offer of treatment.” Those who are not randomly selected to an offer of treatment, are not told about treatments that they have not been offered, as per the Zelen design. The process then proceeds in a similar manner to the Zelen design. Schematics of the Zelen design and the cmRCT design are shown below (Figure 6-2 and Figure 6-3).

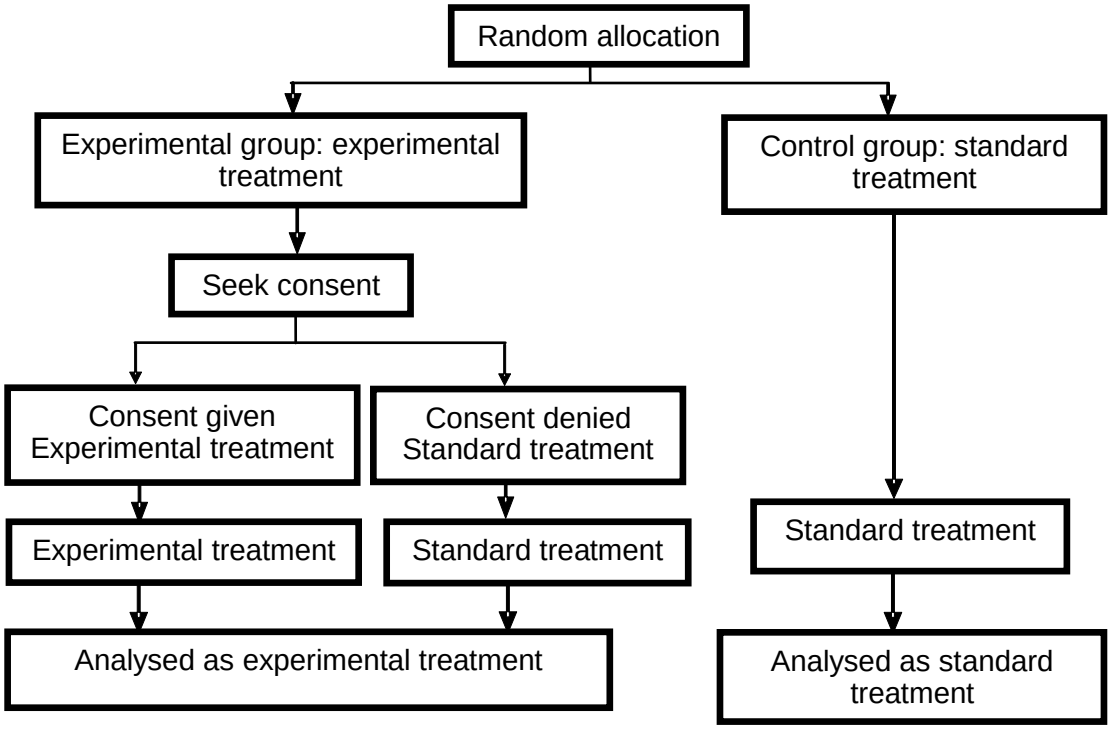

Figure 6-2: Schematic diagram of Zelen design

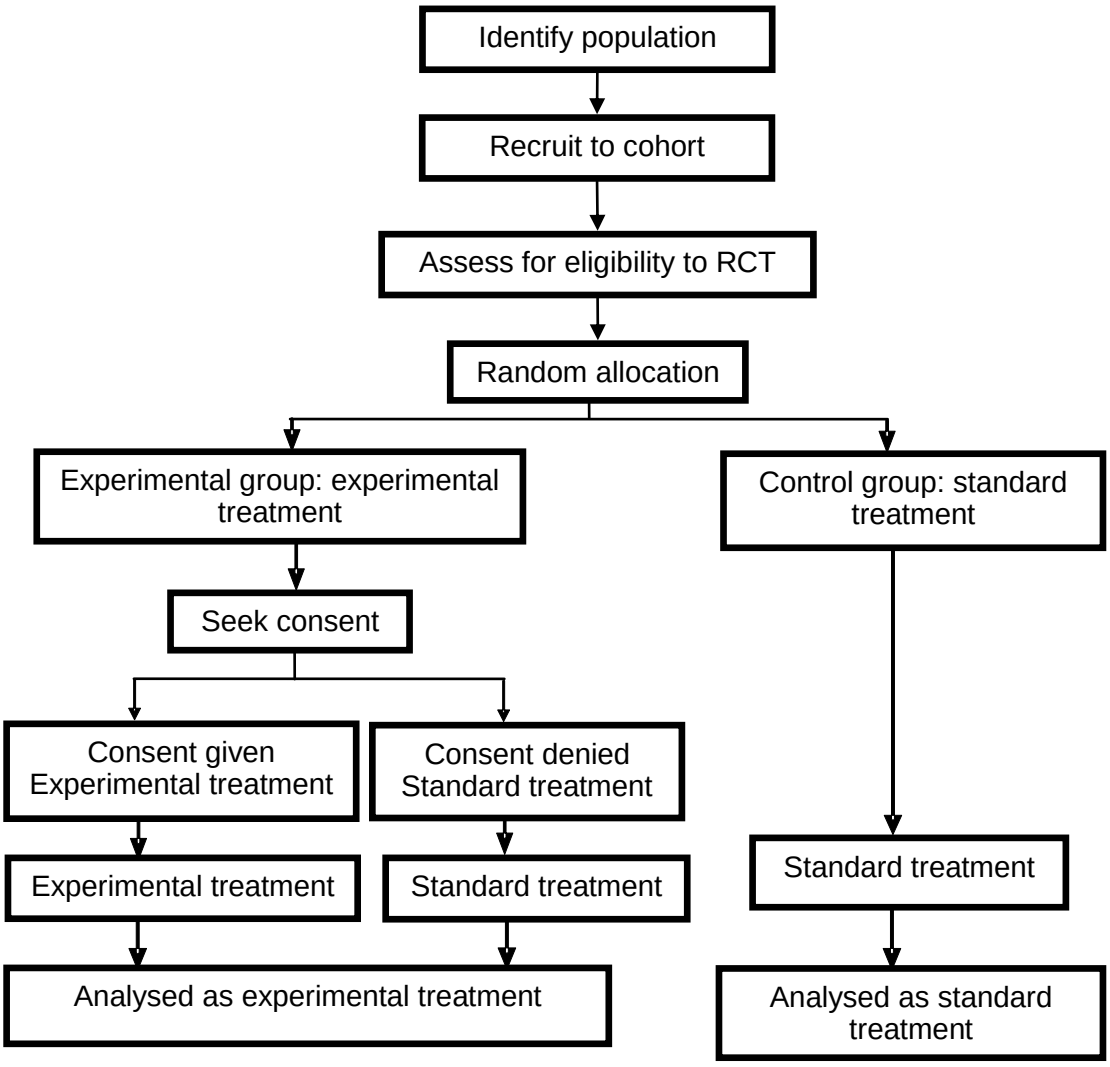

Figure 6-3: Schematic diagram of cmRCT design

In both designs if an intention to treat analysis is being used then everybody who was offered the experimental treatment is analysed as being in the experimental treatment group. This is regardless of whether they consented to the experimental treatment (Zelen 1979; Relton *et al.* 2010).

An important difference between the cmRCT design and the Zelen design is the possibility of using the cohort for further RCT studies, with the advantage of being able to directly compare the different RCT studies, obviating the need for indirect comparisons and the accompanying complexities.

The cmRCT design was chosen over the Zelen design for this study because baseline data was needed for all participants. This was to allow the baseline characteristics of the participants to be compared across the three arms to check that the randomisation had worked in terms of baseline comparability. Any differences could then be adjusted for in an adjusted

analysis, see Chapter 7 for a further discussion on statistical analysis. Obtaining this baseline data would not be possible using the Zelen design, whereas in the cmRCT design, because participants have consented to fill in questionnaires at various time frames, baseline data can be obtained from these questionnaires. In addition baseline data was needed for the cost effectiveness analysis to be carried out as part of the wider trial.

Participants could have been recruited and randomised in the same way as in a “standard” randomised trial where consent is sought from eligible participants, and following consent they are randomised to one of the arms of the trial. However the cohort design was the preferred option for the study team for the wider trial. There are pros and cons with both the standard RCT and the cmRCT design. The cmRCT design aims to replicate real world health care where participants are not told about treatments they are not going to receive (Relton *et al.* 2010). The advantage of participants not being told about treatments they are not being offered, apart from replicating real world healthcare, is that there is less chance of resentful demoralisation. Resentful demoralisation is where participants assigned to the control group become resentful for not receiving the experimental treatment (the usual case) or when participants in the experimental group become resentful of the control group, e.g. if the experimental treatment is perceived as inferior to the control treatment (Torgerson and Torgerson 2008). Resentful demoralisation can result in non-compliance or withdrawal from the trial. A disadvantage of the cmRCT design is that, because participants are not told about treatments they may receive, they may agree to be in the cohort but not actually be interested in receiving any treatment for their condition. This may then lead them to not taking up the treatment they are offered. Whilst this is what occurs in real life, this may not be desirable in a trial assessing the effectiveness of an intervention, unless the aim of the trial was to assess the effectiveness of the intervention in the real world. This means that neither of these options is perfect. As the cmRCT is a recent design and so far only one published trial has used this method (Relton 2009), this study will be able to provide further information about how the cmRCT model works in practice. The IBS cohort recruited for this study was termed the Barnsley Irritable Bowel Syndrome Cohort or BIBSC.

6.1.5 The placebo tablet

As discussed in Chapter 5, to provide structural equivalence between the IHT arm and the supportive listening arm, including a placebo tablet in the

supportive listening arm was considered. However as mentioned in Chapter 5, the inclusion of a placebo tablet has an ethical dimension. This section provides a more focussed discussion on ethics of including a placebo tablet in the RCT.

The definition of a placebo in the Oxford English Dictionary is *" a medicine or procedure prescribed for the psychological benefit to the patient rather than for any physiological effect"* (Oxford Dictionaries 2011). With the implication being that it is the patients belief that the "placebo" will help them that leads to any benefits, rather than some inherent activity of the medicine or procedure themselves. The rationale for the inclusion of the tablet was to serve the purpose of making the IHT and supportive listening as equivalent as possible by ensuring that both arms contain the beliefs and expectations that being prescribed a medication entails. Secondly it would help to ensure that patients return to collect their medication, thus returning for their supportive listening consultations.

In the searches for ACs detailed in Chapter 5 a RCT studying non-cardiac chest pain (Jones et al., 2006) was identified that compared hypnotherapy to supportive listening plus a placebo tablet. The authors justified the inclusion of the placebo tablet as being to boost any placebo effects in the supportive listening arm. The inclusion of a placebo tablet in a trial of IHT could be used to provide structural equivalence between IHT (where the patient receives a homeopathic remedy) and supportive listening. In this case both groups would receive time and attention from the therapist plus a medication, be it placebo or otherwise. The tablet used for the placebo could be sac-lac, the base tablet for homeopathic remedies (consisting of lactose plus a binder), therefore the tablet would appear the same as a homeopathic remedy. However the inclusion of a placebo tablet in the supportive listening arm leads to a question regarding what to tell participants in the supportive listening arm to ensure that the researcher's duty to provide informed consent is met (World Medical Association 2008). In one previous trial the participants in the supportive listening arm were told they were being given "a medication that may help their condition" (Jones et al., 2006). The "medication" in question was an inert tablet and none of the patients were given an active medication (Whorwell, 2010). Ethically this can be difficult to implement because it could be argued that the participants are being misled. In a discussion on this issue Whitehead (Whitehead, 2004) page S162, gives the following advice, "to be able to state in the consent form that the

pills could help, at least a few of the patients should receive an active drug." The theory being that the patients given the active medication would be receiving a medication that might help and everyone in that arm of the trial would have a chance of receiving the active medication. However what Whitehead doesn't explain, or explore, is what people would be told about the tablet they would receive. If they were told "you have x chance of receiving an active medication and x chance of receiving a placebo," and the chance of receiving an active medication was very low, the overall "placebo effect" of the tablet could be reduced, when compared to an arm where everyone is told they were being given a "medication that may help them". Thus there is a possibility that this reduction in overall "placebo effect" could negate any advantage in including the placebo tablet. However, if they were simply told that they would receive "a medication which may help their condition," with the thought that including an active medication makes this statement true, and therefore fulfils the requirement for informed consent, it is difficult to see how this would be any different to not including the active medication. This is because it is believed that Whitehead's suggestion fails to take into account the fact that placebos can be effective (Beecher, 1955). Therefore it would not be misleading to say that the placebo tablets could help, as there is the possibility the tablets could help, either because people believe that taking a tablet might help, or because they are told they might be effective.

The approach of giving some people an active medication was considered, however giving an active medication to some participants would lead to an increase in the number of participants required in the supportive listening arm. This is because the supportive listening arm would now consist of the number of participants calculated in the power calculation (who would be given supportive listening plus placebo) plus the extra people who would be given supportive listening plus active medication. Increasing the number of participants in the supportive listening arm was considered not to be feasible due to the funding limitations of the trial.

Another thought was that the patients in the supportive listening arm could be given a low-dose multivitamin. This would be unlikely to improve their condition but it could be described as "a medication that may help your condition." And thus potentially still act as a placebo – but it may not be inactive and thus not in fact a placebo. Furthermore introducing a multivitamin would lead to the introduction of a new variable into the trial.

This is becasuse it is not known whether a multivitamin would have an effect on IBS. Therefore the supportive listening arm could then be getting an active medication that those in the homeopathic arm would not be getting. It was decided that it was better to keep the trial as simple as possible rather than introducing more variables which can lead to difficulty in analysis. Thus, although having the placebo medication would provide structural equivalence, substituting it with something that could prove to be an active treatment in its own right could over-complicate matters. The potential difficulties identified were, in the interpretation of results, where effects may be due to non-specific effects of the treatments, or due to something specific about IHT and or the supportive listening arm (i.e. the multivitamin).

Taking all this into account it was decided that, in the application to the research ethics committee, a placebo tablet would be included in the supportive listening arm of the trial. The rationale for its inclusion would be explained, that is to provide structural equivalence with the IHT arm.

Another factor that was considered was whether whoever was prescribing the placebo tablet would be comfortable in presenting it as a credible treatment. Without this any placebo effects of the tablet could be lost and there would be no point in including it in the trial. Therefore in addition to the ethical questions over giving a placebo tablet, there is also the difficulty as to who would give out the tablets. In trials by Whorwell's group in Manchester (Whorwell, Prior and Faragher 1984; Calvert *et al.* 2001; Jones *et al.* 2006) the placebo has been given by the person providing the supportive listening, however this relied on this person being comfortable in providing the placebo and telling the participants that this is "a medication that may help." In the trial of non-cardiac chest pain (Jones et al., 2006) a research assistant provided the supportive listening. In this trial it was decided that providing ethical approval for the placebo tablet could be obtained, then the people delivering the supportive listening would give out the placebo tablets, and the rationale for the inclusion of the placebo tablet would be explained to the supportive listening providers. However owing to the concerns of the research ethics committee, a placebo tablet was not included in the supportive listening arm. A full discussion for the reasons behind this decision can be found in Chapter 8.

6.1.6 Outcome measures

Primary outcome measure

The primary outcome measure was the IBS Symptom Severity Scoring System (IBS-SSS) (Francis, Morris and Whorwell 1997). The IBS-SSS is a global measure consisting of 5 questions that are scored on a 100 point visual analogue scale. All scores contribute equally leading to a possible total score of 500, with a higher score equalling greater severity (< 175 represents mild IBS, 175-300 represents moderate severity and >300 represents severe IBS). (Francis, Morris and Whorwell 1997)

IBS-SSS was chosen as it is the measure most commonly used to assess improvement in IBS and therefore its use allowed comparison between this and other IBS trials. Furthermore in a systematic review of outcome measures used in clinical trials for IBS it was ranked by Bijerk (Bijkerk *et al.* 2003) as the best outcome measure based on psychometric and methodological properties for a detailed IBS symptom assessment. The Adequate Relief question (Mangel *et al.* 1998) which measures improvement in symptoms with the single question "Did you have adequate relief of IBS-related abdominal pain or discomfort?" was also felt to be a good choice when assessing global symptomatology as an outcome (Bijkerk *et al.* 2003). However it does not give a detailed IBS symptom assessment and cannot be used to assess baseline IBS severity.

With participant burden as consideration, it was decided to use only one IBS specific outcome measure, because an assessment of the baseline IBS symptoms was needed, the IBS-SSS was chosen.

Secondary outcome measures

When choosing secondary outcome measures it is important to consider what additional value they will give to the study. To allow comparability between this and other trials, and in order to identify the most appropriate outcome measures, a search of IBS RCTs that used an AC was conducted in AMED (Allied and Complementary Medicine) (1985 to June 2010), Embase (1996 to 2010 Week 22) and Ovid Medline (1996 to May Week 4 2010). The search terms used were “specific effect”, “context effect”, “irritable bowel”, “irritable colon”, “Spastic colon”, “functional bowel disease” and “functional colonic disease” and the MeSH terms irritable bowel syndrome, colonic disease and functional colonic disease. This search was

conducted in 2010 prior to the choice of the secondary outcome measures. Full details of the search are given in Appendix 5

From the results of this, and consideration as to what additional value the outcome measure would bring to the study, the following outcomes were chosen.

1. Hospital anxiety and depression scale (HADS) (Bjelland *et al.* 2002). Although improvement in IBS is of primary importance, patients suffering from IBS often report a greater incidence of anxiety and depression and lower feelings of general wellbeing than the general population (Ten Berg *et al.* 2006). Therefore any improvement in these areas could also imply a positive effect of treatment. The scale chosen to assess anxiety and depression was the hospital anxiety and depression scale (HADS). Although there are a variety of scales that can be used, HADS is a validated measure for assessing anxiety and depression and its use in IBS trials is well documented (Kennedy *et al.* 2005; Lu *et al.* 2005; Smith 2006). Coupled with this is the fact that HADS is a self report measure, takes a short time to complete (2-5 minutes), and can be used to assess both anxiety and depression, rather than solely depression or solely anxiety (Snaith 2003).

2. EuroQol-5D (EQ-5D) (Williams 1990). The EQ-5D is a standardised instrument used to measure health related quality of life. It consists of two parts, the first being five questions (dimensions), used to explain a person's state of health for each dimension and the second, a visual analogue scale used by the patient to score their overall health. This was chosen because it was considered that including a global measurement scale to assess whether participants' general wellbeing improved would give valuable information. It was also needed for the cost effectiveness element of the RCT, which is outside the scope of this PhD study. Although there are disease specific quality of life measures available for IBS, such as the IBS quality of life measure (IBS-QoL) (Patrick *et al.* 1998), these do not provide the information needed for the cost effectiveness element of the wider trial. To reduce participant burden in filling out questionnaires it was decided to choose only one health related quality of life measure. There are alternative health related quality of life measures that could have been chosen such as the SF6 D (Brazier *et al.* 1992). However the EQ-5D was chosen over these because it is short, therefore reducing participant burden in completing questionnaires, and widely used, thus allowing comparability of other treatment trials for IBS.

For patients in the IHT and supportive listening arms the following additional outcomes were collected by postal questionnaire at 6 months.

3. Consultational and Relational Empathy (CARE) (Mercer *et al.* 2004). CARE is a measure of the practitioners empathy as perceived by the patients. This was included to explore further the concept of time and attention, give some indications about how patients perceived the therapists, and allow an exploration as to whether there was any correlation between participants' perceptions of the therapists and outcome.

4. Expectation of benefit: This measures the patients expectation of benefit and credibility based on a validated measure originally designed by Borkovec (Borkovec and Nau 1972) and modified by Drossman (Drossman *et al.* 2003) for IBS. It was included to assess the credibility to the patients of the two treatments for IBS. Based on a 10 point scale the patient answers the following two questions (i) how confident would you be that this treatment would be successful in reducing your bowel symptoms? (ii) How logical does this type of treatment seem to you for helping bowel symptoms? The intention was to measure this after the second appointment for those in the active treatment arms. This measure was chosen because the use of Borkovec and Nau's credibility scale is recommended in order to test the integrity of trials of psychological interventions (Irvine *et al.* 2006). However it was considered that Drossman's modified version for IBS would be more suitable than the original version.

5. Each participant's exposure to treatment was recorded e.g. the number of sessions with either a homeopath or "supportive listening" provider.

Exposure to treatment was recorded to allow the uptake of both treatments to be compared. It may have been that uptake was far greater for one of the treatments, which could have been due to:

- Patients feeling better and therefore requiring less sessions.
- Patients not finding the treatment acceptable/useful and so failing to come back for follow-ups.

If was also thought that, if no significant difference in the outcomes was found between IHT and supportive listening, it would be useful to note whether either of the two options was more acceptable to patients than the other.

6.2 Qualitative Interviews

This section discusses the methodology used for the qualitative part of this study. It begins with explaining the rationale behind including a qualitative element and the reasons behind choosing to carry out semi-structured interviews. It then moves on to discuss the aims and objectives of this study and how these influenced the sampling strategy, interview schedule and analysis method.

6.2.1 Why include a qualitative element

To provide the optimum understanding of the effects of complex interventions, such as IHT, a combination of quantitative and qualitative research methods are sometimes used (Walach *et al.* 2006). This is because RCTs are able to give information about whether or not a treatment is clinically effective but they cannot give information as to why this is the case. Therefore in order to better understand aspects of complex interventions qualitative interviews nested in trials have been used to provide information that can not be picked up by the trial outcome data (Thompson *et al.* 2011; Brien, Leydon and Lewith In press). Verhoef et al (Verhoef, Casebeer and Hilsden 2002) argued that including a qualitative element exploring patients' experience of CAM treatment should be considered when conducting CAM research. This is to aid the understanding of why the intervention may work, such as how the patient's beliefs and expectations influence the treatment "working" and what patient's understanding of a treatment "working" is. To this end one particularly useful approach is to nest qualitative studies within a RCT (Bernie 2003).

In this study, the RCT will be able to examine whether IHT is similarly effective to supportive listening, when compared against standard care, however it will not be able to say why this is or isn't so. To better understand the effects of IHT, it would be informative to explore the patient's perspective of what it was about the treatment, if anything, that they perceived to have helped them. A qualitative element to this study would be able to explore whether the patients believed the homeopathic remedy exerted any effects or whether there something inherent in the way the homeopathic consultation was conducted that they found particularly helpful. Did being listened to help them? Or was it something else? In order to create a fuller

picture the therapist's point of view could also be investigated. This would seek to understand how they perceived the treatment to have helped (if it helped) and during analysis determine whether they had a similar perspective to the patients.

One method of carrying out this qualitative work is to conduct in-depth qualitative interviews with participants and therapists from both treatment arms of the RCT. Individual interviews offer the possibility of gaining a deeper understanding into what the patient perceived to have happene along with the ability to pick up nuances of the treatments that cannot be picked up by questionnaires (Rubin and Rubin 2005). Another option would have been to record the homeopathic consultations and the supportive listening consultations and analyse them using a form of conversation analysis. Conversation analysis is the study of conversations with its focus being on the processes involved in social interaction and how talk makes things happen (Greenhalgh *et al.* In press). It aims to understand how specific actions are achieved through talking, e.g., asking questions, providing advice, eliciting symptoms histories, rather than exploring participants understanding of how treatments worked or didn't work (Drew, Chatwin and Collins 2001). Moreover conversation analysis cannot provide information about what people think. Instead it aims to understand communication within the interaction (such as a consultation) and how opportunities for participation are opened up or closed down. It would therefore not answer the questions posed by this PhD study whose aim is to explore the participants' views on the treatment they received. Another option would have been to use focus groups, however focus groups are more suited to situations where the intention is to understand participants attitudes and where interactions between participants will help understand the research issue (Ritchie and Lewis 2003). Individual interviews are more able to gain detailed information on individuals reports, with a greater opportunity for clarification and deeper understanding, especially of complex systems (Ritchie and Lewis 2003). Accordingly in-depth individual interviews were chosen.

The nature of the interview then needed to be decided; structured, semi-structured or unstructured. Unstructured interviews are used to gain a general flavour of participants views or experiences of a topic whilst structured interviews are used when the researcher is interested in one core idea (Rubin and Rubin 2005). This study required more than just a general

flavour of participants' views, but was not just interested in one core idea, such as the participants' views of the remedy. Consequently individual semi-structured interviews were chosen as a means to explore patients views on their treatment and gain a deeper understanding of what the patient perceived to have happened. Furthermore semi-structured interviews allow the same general areas of interest to be explored with each interviewee, whilst at the same time allowing a degree of flexibility to go with the participant rather than adhering strictly to the same pre-prepared list of questions with each participant, as is the case with structured interviews. Carrying out these interviews also had the possibility of adding to the body of knowledge regarding IHT. Previous studies have tried to assess the elements of the consultation from the homeopath's perspective (Eyles *et al*. 2010), and from the participant's perspective (Brien, Leydon and Lewith In press). However so far no studies have been carried out that explore the patient's or the homeopath's perceptions of the whole intervention of " IHT." i.e. explored the perceptions of both the homeopathic consultation and the remedy, and what aspects of these led to any benefit.

6.2.2 Research question

What, if any, elements of their treatment do patients and therapists in the Barnsley Irritable Bowel Syndrome Cohort (BIBSC) study perceive as leading to changes (or lack of) in their IBS and general health?

6.2.3 Aim of the study

To explore patients views of what they found helpful about the treatment they received, and what led to changes in their IBS and general health, in a purposive sample of patients who received IHT, and a purposive sample of patients who received supportive listening.

To explore therapists' views of what patients found helpful about the treatment they provided, and what they perceive to have led to changes in the IBS symptoms and general health of patients taking part in the RCT.

6.2.4 Objectives

In order to answer the research question this research therefore explored the following questions:

For patients

- Whether any aspects of their IBS or general health had changed during their treatment

- What they thought had led to these changes
- What elements of their treatment they thought helped /didn't help
- What the patients liked/didn't like about the treatment they received
- Whether they felt the treatment worked for them
- What their understanding of a treatment working is

For therapists

- Whether they felt the IBS symptoms or general health of the patients had changed during their treatment
- What they thought had led to these changes
- What elements of the treatment they provided they thought had helped /didn't help
- Whether they felt the treatment they provided worked
- What their understanding of the treatment they provided working is.

6.2.5 Construction of a topic guide

Semi-structured interviews offer the possibility of exploring IHT from the patient's perspective, thus gaining an insight into what they feel has helped or not helped them (Rubin and Rubin 2005). Semi-structured interviews can be used to gather patients' perspectives on the different elements to be explored and whether or not they feel it is one particular aspect of the treatment that helped or whether it was the whole package (King and Horrocks 2010). To this end a topic guide to the areas of questioning was needed (King and Horrocks 2010). To allow flexibility in the interviews the topic guide covered broad areas that needed to be addressed rather than focusing in on specific questions (Rubin and Rubin 2005). The aim of the qualitative part of this study, was to explore patients' and practitioners' views of what they felt was helpful about the treatment they received (or provided), and what led to any changes in their or their patients IBS and general health. Therefore, the questions were seeking to explore whether the treatments were helpful, in what way the treatments were helpful, and what it was that led participants to their conclusions. Table 6-1 shows the broad questions that were asked and what each question is seeking to understand.

Question	Area to be explored
Tell me about the treatment you received	Opening question to elicit the patients' initial views.
What changes have there been since you started the treatment? What do you think has led to the change?	To determine if there had been any change. If so what the participant perceived had led to the changes. Did they perceive the change to be due to the treatment they received or something else that has happened in their life? Did they attribute it to a particular aspect of the treatment?
Did you feel the treatment worked for you? If yes, in what way did it work? (Ask for examples). If no, what would the treatment working have been?	What were the participants' perceptions of a treatment working? Did they perceive the treatment to have worked for them? (The participants symptoms may have changed since starting treatment, but a change in symptoms may not be perceived as a treatment working).
What did you find helpful/unhelpful about the treatment? (Ask for examples)	The patient may not have felt the treatment worked as per their definition of a treatment working but they may have found the treatment helpful. What did participants perceive as a treatment being helpful and did they equate a treatment being helpful with a treatment working? They may have been better able to cope with their IBS following treatment even though the symptoms themselves may not have changed.
What did you like/dislike about the treatment?	To explore without explicitly asking whether they enjoyed spending time with and talking to an empathetic practitioner, was this important to them? Was there anything they disliked about the treatment, did those who disliked aspect(s) of the treatment do worse than those who didn't?
Would you use this treatment again? Why?	Did the participant feel strongly enough about the treatment to use it again, is it something they would recommend? They may feel better but would not use the treatment again, if not why not?
What expectations did you have of the treatment? Did it meet these expectations? Did the therapist give you idea of what you could expect from the treatment?	To understand the participants' expectations and any expectations that the therapist gave them. This was mapped with the RCT results to see if there was any relationship between expectations and outcome.
How would you describe the therapist?	To gain an insight into the participants' perceptions of the therapist and whether this related to whether they felt the treatment worked or whether they felt the treatment was helpful. The aim being to better understand the relationship between the participant and the therapist and the impact this had on whether a treatment works
Did the therapist suggest any lifestyle changes or other therapies? Did you follow this advice? What was the outcome?	To find out whether the therapists made other lifestyle suggestions and whether the participant felt these were helpful? Were any improvements down to advice given by the therapist rather than specifically due to the treatment they'd received?
In IHT arm: What was your experience of taking the remedy?	To explore the participants perceptions of taking the remedy. Was the remedy related to any of the changes or was it something else about the treatment such as the talking aspect?

Table 6-1: Interview questions and what they were seeking to explore

6.2.6 Sampling strategy and size

The aim of quantitative sampling methods is to obtain a representative sample of the population being studied thus allowing results to be generalised back to that population. However the aim of qualitative sampling is different (Thompson 1999). Qualitative research sets out to understand issues relating to human behaviour, and therefore requires a sample that is likely to cover all the areas of interest, from as broad a range of standpoints as possible, from a sample that addresses the particular needs of the individual question (Mays 1996). There are different types of sampling that can be used. Convenience sampling, as its name suggests seeks to sample the most accessible members of the population being studied (Mason 1996). Whilst theoretical sampling requires the building of theories from the emerging data and then selecting a new sample which will allow the theory to be explored and elaborated further (Ritchie and Lewis 2003). Finally in purposive sampling the researcher actively selects a sample of people that are likely to cover the range and diversity of experiences. A sampling frame is often used to aid this (Ritchie and Lewis 2003).

In this study it was intended that a purposive sample of approximately 16 patients would be interviewed, 8 people from each of the two active treatment arms of the trial. Purposive sampling was chosen because this research is setting out to understand how different people viewed the treatment they received. It is not setting out to develop a theory or theoretical model of the treatment, rather it requires a range of experiences and views. It was planned that a sampling frame (see Section 6.2.7.2) would be used to purposively select participants to ensure that the data reflected the range and diversity of treatment experience. The RCT aimed to recruit 33 people to each arm. It was estimated that with loss to follow up, potential under recruitment, and ineligibility to take part in the interviews, there would be roughly 20 people in each arm of the trial eligible to take part in the interviews. Therefore to gather the range of people identified in the sampling frame it was expected that it would be sufficient and feasible to recruit 8 people from each arm.

Four therapists provided treatments as part of the BIBSC study, two providing supportive listening and two providing IHT. To reflect the diversity of therapists' experiences it was the intention was to sample all four therapists.

In summary the sample size was decided on based on the following criteria:

- It was anticipated that this number would generate data with sufficient breadth and depth to give enough information for key themes in people's experiences to be identified.
- It would be feasible to undertake given the constraints of time and resources for the study.

6.2.7 Participants

6.2.7.1 Inclusion and exclusion criteria

To be included in the sample participants must have taken part in the RCT.

Inclusion criteria for patients

- Participated in either the supportive listening or IHT arm of the RCT. This is because the interviews were focusing on peoples experiences of their treatment in the RCT.
- Attended at least 2 treatment sessions. Participants will need to have experienced at least two sessions to understand what the treatment they were offered involved.

Inclusion criteria for therapists

- Provided either supportive listening or IHT in the RCT because the interviews focused on therapists views of the treatment they provided in the RCT.

6.2.7.2 Sampling frame for patients

The intention was that participants who met the above inclusion criteria would be purposively sampled from each of the two active treatment arms. This was to ensure that there was a mix of people who experienced benefit and who did not experience a benefit, from each treatment arm of the RCT. It was also planned to recruit a mixture of men and women. This was because it was thought that men may have a different perspective of treatment to that of women. A previous study comparing IBS patients managed in primary and secondary care, found despite there being a greater number of female IBS sufferers, one of the factors associated with consulting in secondary care was being male (Smith *et al.* 2004). Therefore it is likely that there is some difference associated with gender in the treatment of IBS. Table 6-2 shows the sampling frame for this study.

Treatment	IHT n=6-8			
Gender	Male n=3-4		Female n=3-4	
Did the treatment work?	Yes n=1-2	Maybe/No n=1-2	Yes n=1-2	Maybe/No n=1-2
Treatment	Supportive listening n=6-8			
Gender	Male n=3-4		Female n=3-4	
Did the treatment work?	Yes n=1-2	Maybe/No n=1-2	Yes n=1-2	Maybe/No n=1-2

Table 6-2: Sampling frame for interviews

Treatment is defined as having worked if following treatment the patient has a decrease of 50 or more in the IBS symptom severity score (Francis, Morris and Whorwell 1997).

Due to a lower than anticipated recruitment into the RCT the number of participants in the IHT and supportive listening arms of the trial were too low to purposively sample. Therefore an amendment was sent to the research ethics committee. Permission was given to invite to interview all those who had attended at least two IHT or supportive listening consultations. A copy of this permission letter is given in Appendix 10.

6.2.8 Analysis method

The choice of analysis method is influenced by the aims and objective of the research, what the research findings are intending to do and the researcher's own philosophical stance (Richards 2005). In this study the findings are intending to provide a greater understanding about what participants' believed to have been helpful about treatment, and what, if anything they believed to have led to an improvement in IBS symptoms and/or general health. In this case the aim is not solely to report the views of the respondents but to provide an understanding of how the participants came to their conclusions.

Framework analysis is a method developed for use in the area of applied policy research (Ritchie and Spencer 1994). In applied policy research the objectives are set by specific requirements. This means that the results of the research are targeted to give answers that provide a greater explanation

or understanding of the issues being addressed. In addition the timescales in applied policy research tend to be relatively short being months not years. Hence framework has been developed to fit these criteria (Ritchie and Spencer 1994).

Framework was chosen as the analysis method for this research. This is because the main aim of the research involved providing an understanding of participants' views rather than trying to generate a theory about participants' views. In grounded theory, the aim is to use the data to produce a plausible theory, grounded in the data (Braun and Clarke 2006). In addition to this, grounded theory requires an iterative process of data collection and analysis, whereby the results of the initial data collection are used to inform further sampling. This is followed by further analysis and checking of the theory being generated until saturation is reached (Richards and Morse 2006). Saturation occurs when no new ideas are brought up in the data collection process (King and Horrocks 2010). The structure of this qualitative study did not allow for such a process. Therefore framework was felt to the most appropriate means of analysing this study.

As far as possible throughout the conduct of this research the author has attempted to take the stance of the unprejudiced observer. The position of the unprejudiced observer requires acknowledgement that whilst it is impossible not to have any prejudices, through being aware of one's prejudices, and questioning one's self and one's thoughts and actions, one can aim to perceive without projection (Vithoulkas 1998). A fuller discussion of this and the impact it has had on this research can be found in Chapters 8 and 10.

This chapter described the methodology for both the quantitative and qualitative studies, explaining how this PhD study related to a wider trial of the clinical and cost effectiveness of IHT for IBS, along with a rationale for why the cmRCT design was used. The option of including a placebo tablet in the supportive listening arm of the trial was explored and the choice of outcome measures explained. The RCT will be able to give information about whether or not IHT works, but it will not be able to say why this is so, hence it was decided that a qualitative element should be included in this study. This chapter explored in more detail the reasons behind this decision and explained why semi-structured interviews were chosen and the reasoning behind the sampling strategy and interview schedule. The next

chapter details the methods for both the quantitative and qualitative studies and explains how each of these studies was carried out.

7 Methods

This chapter describes the methods used in both the RCT and the qualitative study. It explains how the studies were conducted, following on from the previous chapter which explained why the studies were conducted in the way they were. This chapter is split into two sections, a section on the methods for the RCT and a section on the methods for the qualitative interviews.

7.1 Randomised controlled trial

7.1.1 Design

A full description of the design of this study is given in Chapter 6, whilst an overview of the design is given here. This study is a three armed prospective, parallel group, individually randomised trial comparing:

- Usual care alone
- IHT plus usual care
- Supportive listening plus usual care

The study used the Cohort Multiple RCT Design (Relton *et al.* 2010). A discussion on the features of this design in given in Chapter 6.

In this study eligible participants who consented to take part in the observational study made up the Barnsley IBS cohort (BIBSC). From the BIBSC some people were randomly allocated to the “offer of intervention” (IHT or supportive listening) or to the usual care arm of the trial. The recruitment and randomisation processes are discussed in more depth in Section 7.1.4.

7.1.2 Treatment

Patients allocated to either the IHT or the supportive listening arm were offered five consultations, one every five weeks for five months. The consultations were spaced at these intervals because in usual homeopathic practice patients will be seen every four to six weeks. Patients were offered five consultations because it is generally considered, by homeopaths, that on average patients will need this number of consultations for a measurable benefit to be observed. The consultations for both IHT and supportive listening were 60 minutes. Thus each of these two arms received the same amount of direct face-to-face contact with a therapist (if they attended all appointments). Figure 7-1 shows the treatment and data collection schedule. Usual care included any drug treatments or other supportive regimes that an NHS patient with IBS would usually have access to.

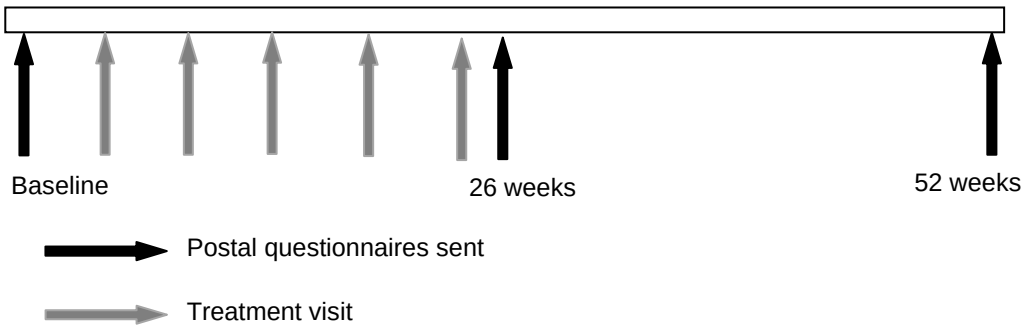

Figure 7-1: Treatment and data collection schedule

Both homeopaths and supportive listening therapists were supervised by supervisors with an allegiance to that therapy. This means that homeopaths were supervised by supervisors who are also homeopaths and supportive listening therapists were supervised by counselling supervisors.

7.1.2.1 Individualised homeopathic treatment

Two homeopaths with a 5 year history of working at Barnsley Hospital delivered the IHT. They were both registered with the Society of Homeopaths (SoH) and had previous experience of trials of IHT. Clinical homeopathy and IHT have different prescribing strategies, however both homeopaths involved in this study are classical homeopaths (IHT practitioners) and are registered with the Society of Homeopaths. The homeopaths were able to choose from any of over 1,300 different possible remedies from the homeopathic pharmacopeia.

7.1.2.2 Supportive listening

Supportive listening was delivered by qualified psychotherapists with at least five years clinical experience, employed by Barnsley Hospital NHSFT, chosen as having a warm empathic manner likely to foster a positive relationship between them and the patient. There were no nurses or similar health professionals that had been trained in basic counselling skills based at Barnsley hospital available, and it was a requirement from the local research ethics committee that the people providing the supportive listening were members of the British Association for Counselling and Psychotherapy (BACP) or the United Kingdom Register of Counsellors and Psychotherapists (UKRCP). During the supportive listening session patients were able to talk about their physical symptoms as well as any emotional issues and possible ways of coping with these better. Supportive listening provided the patient with the opportunity to feel heard and with the opportunity to express themselves in a non-judgemental environment. Participants were encouraged to talk about their physical symptoms as well as any emotional issues and to discuss how these might be coped with in a better way.

Prior to the commencement of the trial counsellors who were interested in providing the supportive listening were interviewed and the nature of the intervention explained to them. After the two counsellors had been recruited to the study there was a further session where the nature of the supportive listening intervention was reiterated. At this point they had the opportunity to ask any questions about what was expected of them.

It was the intention that a check would be carried out to ensure that the counsellors delivering the supportive listening were delivering supportive listening rather than cognitive behavioural therapy (CBT) or some other

psychotherapeutic intervention. This was to be done by assessing a random selection of the taped supportive-listening sessions. In this check the assessor would be looking for instances where the counsellor used techniques that did not fall within the supportive listening criteria such as interpreting information rather than responding reflectively.

7.1.3 Inclusion and exclusion criteria

There were two levels of inclusion in the wider trial, inclusion in the BIBSC and inclusion in the RCT. This thesis is concerned with the RCT, however to meet the inclusion criteria for the RCT the participants need to have first met the inclusion criteria for the BIBSC study. Hence the criteria are described below.

Inclusion Criteria for BIBSC study

- Irritable bowel syndrome diagnosis according to ROME III diagnostic criteria for IBS. This is the criterion commonly used to define IBS in treatment trials.
- Adults aged 18 and over.
- Consent to take part in the BIBSC Study.
- Able to understand written English.

Everyone who completed a questionnaire and met these inclusion criteria was eligible for the BIBSC study. Those eligible for the BIBSC study were then assessed to determine whether they met the inclusion and exclusion criteria for the RCT. Due to the potential for the BIBSC to be used for future RCTs exploring IBS the inclusion criteria were broad. Thus, depending on what an RCT was addressing, each RCT that used the cohort could have different inclusion criteria. For example, the RCT in this PhD study was looking at all patients with IBS, but a future RCT may only be interested in patients with diarrhoea prevalent IBS. By having broad criteria for the cohort, different populations can be sampled for each RCT, hence there may be different inclusion criteria for the cohort, and for the RCT, with the latter being more restrictive.

Inclusion criteria for the RCT

- Score of 100 or greater on the IBS Symptom Severity Score, this score is often taken as the cut off for symptomatic IBS.

Exclusion criteria for the RCT

- Current diagnosis of haemophilia or cancer
- Major gastrointestinal surgery in previous 6 months
- Currently receiving homeopathic treatment. If a significant number of participants in the “supportive listening” arm of the trial were already receiving homeopathic treatment, the effectiveness of IHT compared to supportive listening could be underestimated.
- Pregnant or breast-feeding
- Patients not fluent in English. Patients need to be able to converse with the therapist if selected to one of the active treatments.

Apart from “currently receiving homeopathic treatment” and not being fluent in English, these are the standard exclusion criteria used in trials of IBS. These groups are excluded because it is perceived that taking part in a trial may present a risk to people with the above conditions. Whilst it is unlikely that either IHT or supportive listening would cause a worsening of symptoms to the above groups, or any harm to pregnant or breast-feeding women, in the interests of safety it was felt prudent to exclude the above groups.

7.1.4 Recruitment

Patients were recruited through NHS primary and secondary care settings as follows.

Primary care: Potential participants were identified via GP databases, a method used successfully to recruit IBS patients to an acupuncture study (Reynolds, Bland and MacPherson 2008). The intention was that potentially eligible participants would be identified through searching the database of four GP practices for patients aged 18 and over with a diagnosis of IBS or given medications used to treat IBS symptoms and who have consulted their GP for IBS within the last two years.

Secondary care: Potential participants were identified by gastroenterology clinicians at Barnsley Hospital using the same criteria as for the GP database searchers i.e. having a diagnosis of IBS or being prescribed medication used to treat IBS.

All participants remained under the care of their GP and/or consultant. Once identified, potential participants were sent a letter inviting them to take part in the observational study and asking them to complete a questionnaire, which included screening questions according to the ROME III diagnostic criteria.

See Appendix 6 and 7 for copies of the GP letter, questionnaire and participant information sheet. Once patients returned the questionnaire, if they fulfilled the inclusion criteria and consented, they were entered in to the BIBSC study. Those who were eligible for inclusion into the BIBSC study were then assessed by the researcher and a gastroenterologist to determine whether or not they met the inclusion and exclusion criteria for the RCT.

Figure 7-2 shows a CONSORT diagram of this process (Schulz *et al.* 2010).The completed diagram is given with the results in Chapter 9.

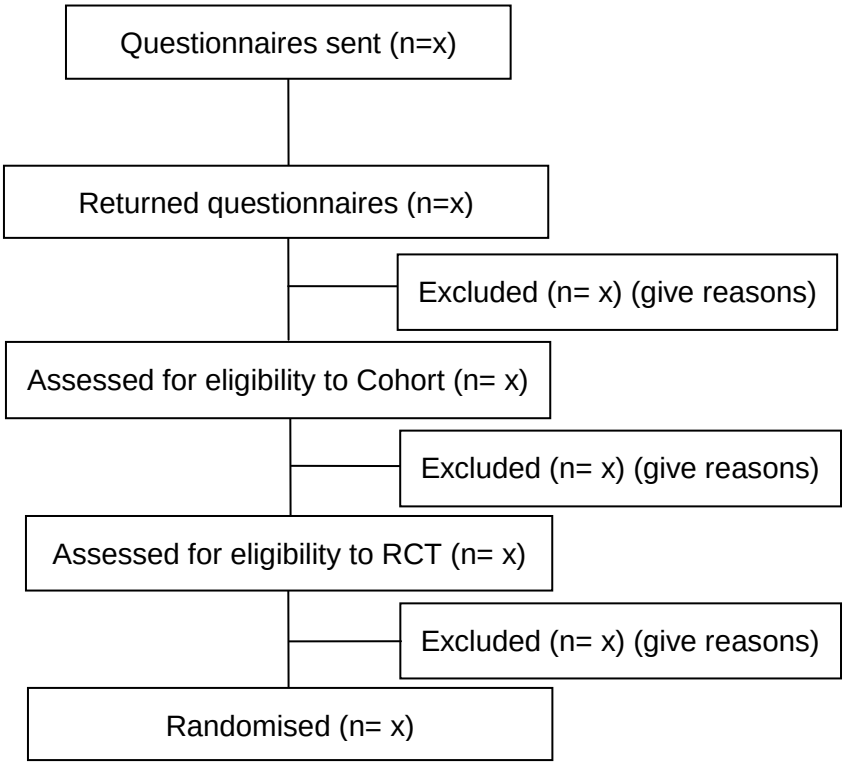

Figure 7-2: CONSORT diagram of the recruitment process

In the RCT there was uneven randomisation to the three arms in a 4:1:1 ratio of usual care alone: IHT plus usual care: supportive listening plus usual care. Due to the limited funding available for this trial, it was decided to use unequal randomisation to reduce the number of participants needed in the treatment arms, thus reducing the overall costs of the treatment arms. The impact of this on the power of the study to detect a difference between IHT and supportive listening is given in Section 7.1.5.

Of those that were eligible for the RCT participants were randomly selected to the offer of IHT, the offer of supportive listening or usual care. The random

selection was achieved thorough the shuffling of a pack of opaque sealed envelopes containing the allocation. Questionnaires from participants who consented and met the eligibility criteria were taken one at a time. At the same time a sealed opaque envelope containing the allocation was taken from the top of the shuffled pack. The envelope was opened and the allocation noted. This was carried out by an independent administrator at the University of Sheffield. It is important that the randomisation process is adequately concealed to prevent selection bias. This occurs when there are systematic differences between the participants in the comparison groups, which can lead to over-estimation or under-estimation of the treatment effect (Torgerson, 2008).

Figure 7-3 shows the relationship between the cohort and the RCT.

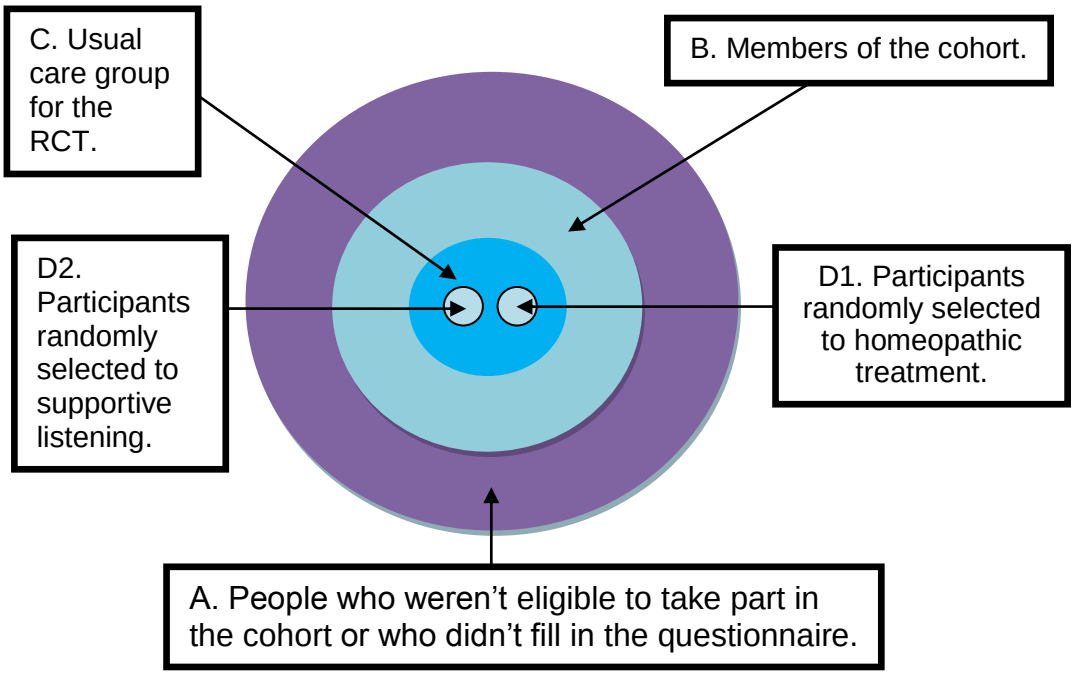

Figure 7-3: Relationship between Cohort and RCT

Those randomly selected to the offer of IHT and those randomly selected to the offer of supportive listening were sent participant information sheets, detailing what the treatment involved, and a consent form to sign (see Appendix 7 for participant information sheets and consent forms). If they signed and returned the consent form an appointment was made for them with the relevant practitioner. Figure 7-4 gives an example of the CONSORT diagram that was used to summarise the data for the randomisation process. The completed diagram is shown in Chapter 9.

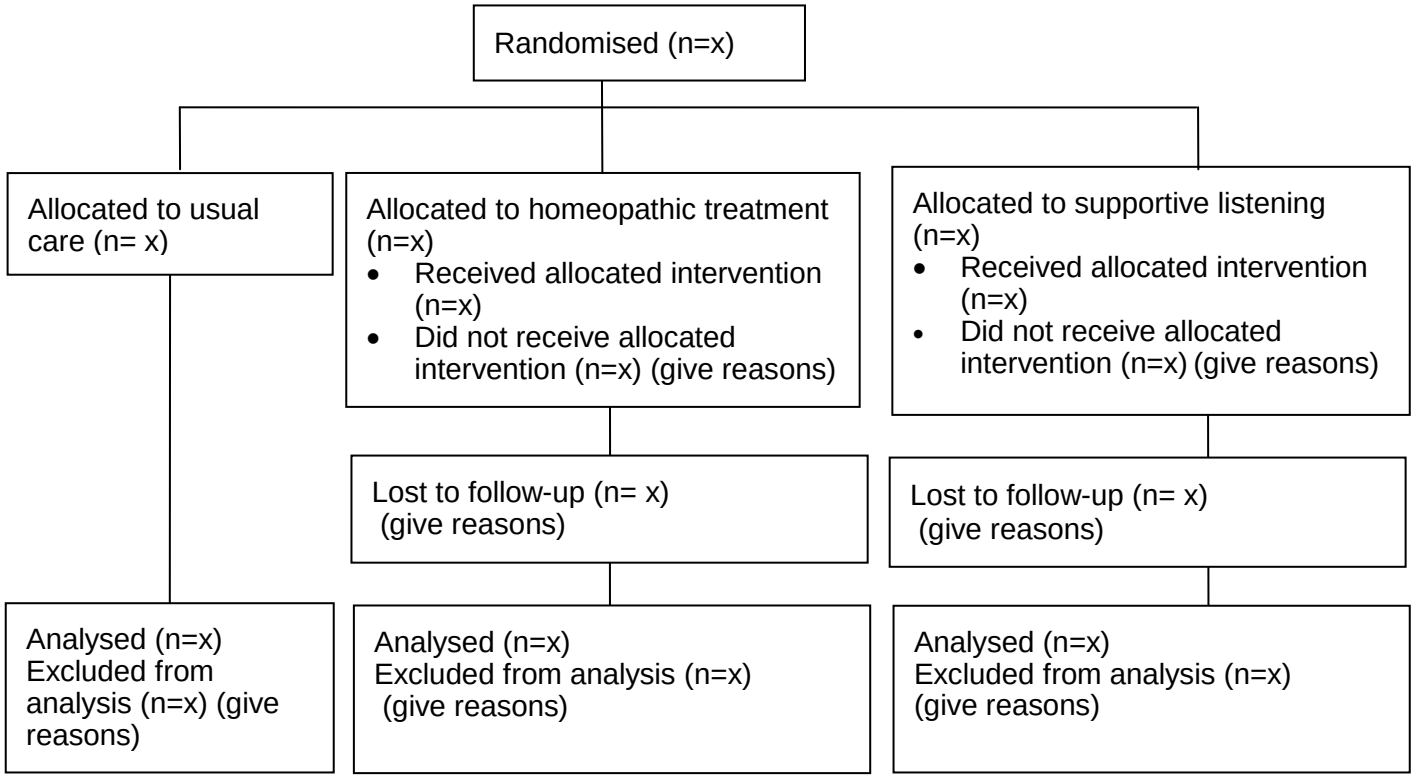

Figure 7-4: CONSORT diagram of randomisation process

7.1.5 Sample size

The sample size calculation was based on the primary outcome for the wider trial, which is the change in IBS-SSS between baseline and 26 weeks (a discussion on why change score was used is given Section 7.1.8.1), with the primary research question for the wider trial being “What is the clinical and cost effectiveness of IHT + usual care compared to usual care alone?” Therefore the primary comparison for the wider trial was between IHT and usual care, thus it was necessary to power the trial to assess whether there was any difference between IHT and usual care, for this reason the trial was powered for an independent t-test between IHT and usual care, for the change in IBS-SSS between baseline and 26 weeks.

As the sample size was powered for the primary research question, which was to compare two treatments using an independent test, the sample size was not based on the global test, ANOVA for comparing more than two groups. A calculation could have been carried out assuming the use of ANOVA taking into account the 3 arms of the trial. This would have led to a smaller sample size but would not have powered the trial for a comparison between the two treatment groups of interest in the primary research question. This is because it would only have been able to power the study to find a difference across the three arms of the trial and not to detect a specific difference between two pre-specified groups (Munyombwe 2010).

A power calculation was carried out using sample size determination software called PS Power (Dupont and Plummer 2009), using a reduction of 50 points on the IBS-SSS, which has been reported to be a clinically relevant change (Francis, Morris and Whorwell 1997). A standard deviation of 85 was chosen. There were no previous trials of IHT for IBS that had used the IBS-SSS. Therefore a statistician was consulted who advised the use of a standard deviation from another similar trial. Three IBS trials that had used the IBS-SSS were used to obtain an estimate standard deviation (Kaptchuk et al., 2008; Moss-Morris et al., 2010; Ringstrom et al., 2010). This was done by taking the average of the standard deviations for the change in IBS-SSS in these three previous trials, which was 85. Assuming use of an independent t-test to compare groups, power 80%, significance level 5%, clinically relevant difference of 50 on the IBS-SSS, and standard deviation of 85, ratio of usual care to IHT of 4:1, 29 participants were required for the IHT arm and 116 for the usual care arm, for this comparison. In a previous IBS study (Reynolds, Bland and MacPherson 2008) it was found that there was a

13% loss to follow up, taking this into account gave an estimated sample size of 33 for the IHT and supportive listening arms and 132 for the usual care arm. In terms of the adequacy of this sample size for adjusted analysis using multivariable regression analysis, the above power calculation leads to a sample size for the IHT arm plus the usual care arm plus the supportive listening arm of 198. To determine the number of regression coefficients that could be used in an ANCOVA the 10 cases per predictor rule of thumb was used. This means that for every predictor used in the ANCOVA model there should be 10 participants who experienced the outcome of interest. This means if the ANCOVA model was used to determine whether there were any differences between the three arms in this trial, adjusting for age, sex and initial IBS-SSS, this would give a total of 6 predictors (including the intercept). Therefore 60 participants would be needed.

A separate power calculation was carried out to determine the sample size required to answer the research question for this PhD study which is “Is individualised IHT any different to “supportive listening” in the treatment of Irritable bowel syndrome?” Based on the previous assumptions, except assuming a ratio of 1 to 1 of supportive listening to IHT and a 13% loss to follow up, a sample size of 53 in the IHT arm and 53 in the supportive listening arm was required.

Due to limited funds it was decided to aim to recruit 198 participants in total, allowing for 33 participants in each of the active treatment arms and 132 in the usual care arm, thus powering the trial to determine if IHT is any different to usual care in terms of reduction of IBS symptoms as measured by IBS-SSS. This meant that the study would be underpowered for the comparison between IHT and supportive listening. However it was intended to proceed while trying to identify additional funding. Hence if sufficient extra funding was secured then the aim would be to recruit 53 people to each of the active treatment arms, thus powering the trial to determine if IHT is any different to supportive listening, in terms of reduction of IBS symptoms as measured by IBS-SSS. A calculation was carried out in PsPower (Dupont and Plummer 2009) to determine what effect size could be detected between IHT and supportive listening with a 1:1 ratio, 80% power, alpha of 0.05 and 33 people in each group. This gave an effect size of 59.53, meaning that with 33 people in each group, the study was powered to detect an effect size of 59.5

or more. This is almost 10 points more than the minimal clinically relevant change of 50, associated with the IBS-SSS.

As previously described in Section 7.1.4, participants were recruited to the BIBSC via primary and secondary care, however an estimate of how many questionnaires to send out was needed. To do this a rough calculation was carried out working backwards from the required sample size for the RCT. As previously stated, a power calculation estimated that the total number of people needed for the RCT was 198.The first step was to use this figure to estimate the number of members the BIBSC would need, in order, that there would be 198 members eligible for the RCT. It was unknown how many members of the BIBSC would meet the eligibility criteria for the RCT, so a conservative estimate of 30% was taken, (the GP database recruitment criteria meant that it was likely that those sent a questionnaire would have IBS, therefore this was conservative). This gave a figure of 660 people. From this figure an estimation was made of the number of people to send a questionnaire to, to result in the BIBSC containing 660 members. Based on a previous study, (Hillila, Farkkila and Farkkila 2010) that achieved a 70% response rate to a postal survey of IBS patients, it was anticipated that, the response rate would be circa 60%. This led to the requirement of a total of 1100 questionnaires to be posted to potentially eligible participants.

7.1.6 Data collection

Data was collected via questionnaires sent to the participants at baseline, 26 weeks and 1 year after sending the baseline questionnaire. However only data collected at baseline and 26 weeks is included in this study. This is due to the time limitations associated with PhD study, and agreement within the team, that the one year data would be analysed separately.

(Details of NHS and resource use as measured by medication and visits to healthcare professionals were also collected to facilitate an economic analysis as part of the wider study.)

Table 7-1 gives details of which outcome measures were collected at which time frames, it should be noted that the 52 week data is outside the scope of this study, however it has been included in the table for reasons of clarity.

	Baseline	26 weeks	52 weeks	Other
IBS-SSS	✓	✓	✓	
HADS	✓	✓	✓	
EQ-5D	✓	✓	✓	
Medication usage	✓		✓	
Number of healthcare visits	✓		✓	
Expectation of benefit				After 2nd appointment in active treatment arms
CARE		✓		
Exposure to treatment				Collected by therapist in active treatment arms

Table 7-1: Time frames at which outcome measures will be collected

7.1.7 Ethical considerations

The ethical considerations for this study were:

- The ethics of conducting trials of homeopathy
- The inclusion of a placebo tablet in the supportive listening arm
- The informed consent process in trials using the cmRCT model
- Adverse events
- Confidentiality and data storage

A full discussion on these is given in Chapter 8.

7.1.8 Analysis

7.1.8.1 Statistical Analyses

Descriptive Statistics

Continuous data was summarised by mean and standard deviation, provided it was normally distributed. Data was tested for normality through plotting histograms of the data. In the case of data not being normally distributed the median and inter-quartile range were quoted. Ordinal data was summarised by median and inter quartile range. Table 7-2 gives details of the data summarised.

		Usual Care	IHT	Supportive listening
Gender	Male			
	Female			
Age	Mean (sd)			
	Missing			
Employment	Employed			
	Unemployed			
	Unknown			
Number of prescribed medicines	Mean(sd)			
	Missing			
IBS-SSS	Mean (sd)			
	Median (IQR)			
	Missing			
HADS-D	Mean (sd)			
	Median (IQR)			
	Missing			
HADS-A	Mean (sd)			
	Median (IQR)			
	Missing			
EQ-5D Global	Mean (sd)			

Table 7-2: Summary of baseline data

Inferential Analyses

The intention was to perform univariate analysis subgroup analysis using independent t-tests or the Mann Whitney U test for change in IBS-SSS between baseline and 26 weeks and change in HADS between baseline and 26 weeks.

It was also planned to carry out an adjusted analysis of change in IBS-SSS between baseline and 26 weeks across all groups, using ANCOVA, with outcome variable; change score and predictors; initial score.

Statistical analyses were performed using PASW Statistics version 17, on an intention to treat basis (ITT) using a 2 sided 5% significance level. intention-to-treat analysis was used to maintain the baseline comparability (Bowers 2008). The challenge of using an intention-to-treat analysis with this type of design is that the people who are offered an intervention may not actually be

interested in having it. This happens in standard randomised controlled trials but the difference with the cmRCT design is that when participants consented to take part in the observational study they weren't consenting to take part in an RCT of different treatments. Thus there may be a greater chance than with a standard RCT of participants not being interested in the treatment offered. Participants not taking up the offer of treatment may lead to a Type II error, where there is no difference found between the treatments when there is really a difference between the treatments, in those who accepted and complied with, the intervention. It was thought likely that the number of people who didn't have the treatment they are assigned to would be higher than in standard RCT, however it was considered that the results would tell the real life 'effect' of the interventions, if allocated and recommended to an unselected population. However high rates of non-use of the allocated intervention may lead to high Type II error rates. This would also indirectly provide information on the acceptability of the intervention to patients.

An alternative to an ITT analysis is a per-protocol analysis. This method includes in the analysis only those who actually had the treatment they were assigned to (Kirkwood and Sterne 2003). For the results of a per-protocol analysis to be unbiased the probability of taking up the treatment must be random, and there should be no other differences between those who took up the treatment and those who didn't, thus ensuring that baseline randomisation is held (Hewitt, Torgerson and Miles 2006). However it was considered likely that in this RCT there could be fundamental differences between those who took up the treatment and those who didn't, meaning that a per-protocol analysis had the potential of being biased. Therefore the baseline data for those who took up the offer of treatment and those who didn't take up the offer of treatment were compared. This was not subject to formal testing but was tabulated and accompanied by a written narrative.

A description of the outcome measures used in this study and the rationale for choosing them is given in Chapter 6.

Primary analysis

The primary analysis was change in IBS-SSS between baseline and 26 weeks.

The percentage of participants in each arm who achieved a decrease in IBS-SSS score of ≥ 50 and the percentage of participants in each arm whose

IBS-SSS score increased by ≥ 50 was reported. A decrease in 50 points on the IBS-SSS is the minimal clinically relevant change for this measure (Francis, Morris and Whorwell 1997).

The reasons for choosing the IBS-SSS as the primary outcome measure are given in Chapter 6. The reasons for choosing change in IBS-SSS between baseline and 26 weeks as the primary outcome are discussed below.

The IBS-SSS is self scored on a series of visual analogue scales (VAS). There is no consensus as to how VAS data should be analysed. Some hold the view that VAS data is ordinal and that it is inappropriate to calculate means and standard deviations for such data (Bowers 2008). Whereas others suggest that means can be used as long as they are used with caution and data is checked for normality (Campbell 1999). On consideration of these two approaches it was decided that the best strategy was to check for normality of the data and then use parametric tests, as long as the data proved to be close to normally distributed, however if this was found not to be the case then non-parametric tests would be used.

There were a number of options for analysing the data, these were:

i) Comparison of 26 week IBS-SSS score's

ii) Comparison of percentage change in IBS-SSS score's from baseline to 26 weeks

iii) Regression model which outcome post-treatment score adjusted for baseline score (Analysis of Covariance) ANCOVA with treatments and other confounders as covariates

iv) Regression model of change score adjusted for baseline and other confounders

v) Comparison of change in IBS-SSS score from baseline to 26 weeks

Theoretically because the participants had been randomised, the average scores in each of the groups at baseline should be approximately equal, therefore any differences found between the groups at 26 weeks should be due to the treatment that they have received. If this was the case the estimated treatment effect would be the same whichever method is used. However Vickers (Vickers 2001) cautions against the use of percent change because it has lower statistical power than both change between baseline and 26 weeks and 26 week score alone. Change score was chosen over end point score because the majority of trials that have used the IBS-SSS

measure have used a change score. Therefore using change score would allow greater comparability between this and other trials. However Vickers (Tu, Baelum and Gilthorpe 2008) suggest a better approach is to use analysis of covariance (ANCOVA), a form of regression which adjusts each person's follow up score for their baseline score, with the advantage of being unaffected by baseline differences. In this study it was intended that both univariate and adjusted analysis (using ANCOVA) would be performed. This would be done to see if whether there are any effects of confounders. If the randomisation had worked then the treatment effects should be similar for both unadjusted and adjusted analysis. Prior to carrying out the ANCOVA analysis the normality assumption was tested using a residual analysis and the residuals checked to ensure that they are independent and had constant variance. This was done using a histogram of residuals and a plot of residuals against plotted values. A residual is the difference between the observed value of the dependent variable and the predicted value of the independent variable (Katz 2006).

Secondary analysis

The secondary outcome measures are:

- Hospital anxiety and depression scale (HADS) (Bjelland *et al.* 2002)
- Consultational and relational empathy (CARE) (Mercer *et al.* 2004)
- EuroQol-5D (Williams 1990)
- Expectation of benefit: based on a validated measure originally designed by Borkovec (Borkovec and Nau 1972) and modified by Drossman (Drossman *et al.* 2003) for IBS.
- Exposure to treatment

A discussion on the reasons for choosing these outcome measures is given in Chapter 6.

Anxiety and depression

Change in HADS between baseline and week 26 was calculated. As with the IBS-SSS there were a variety of options for analysing the data:

i) 26 week HADS score

ii) Percentage change in HADS score from baseline to 26 weeks

iii) Regression model which outcome post-treatment score adjusted for baseline score (Analysis of Covariance) ANCOVA with treatments and other confounders as covariates

iv) Regression model of change score adjusted for baseline and other confounders

v) Change in HADS score from baseline to 26 weeks

In previous trials of IBS change scores have been used (Atkinson *et al.* 2004; Simren *et al.* 2004). A discussion on the use of change scores or endpoint scores concluded that the results were similar in both depending on the nature of the data (Vickers and Altman 2001). Therefore to allow comparability with other trials change in HADS was chosen.

HADS is an ordered categorical (ordinal) scale, in which respondents are asked to tick one answer out of a choice of four possible answers per question. It comprises of 14 questions, 7 of which are designed to assess for anxiety and 7 for depression. Question responses are analysed by assigning numerical scores to the ordered categories, with 0 equating to good and 3 equating to poor. Once numerical scores have been assigned, those scores equating to the depression questions are summed, and those equating to the anxiety questions are summed. A numerical score is then provided for the depression component and another number provided for the anxiety component. Possible total scores range from 0 (the best state) to 21 (the worst state). These summed scores are often treated as if they were from a continuous distribution that is normally distributed (Boyce *et al.* 2003; Atkinson *et al.* 2004) yet as with the IBS-SSS scores it can be debated as to the appropriateness of this assumption. However in this study the same approach as for the IBS-SSS was taken i.e. the data was checked for normality. As long as it proved to be normally distributed the data was treated as continuous and parametric tests were used. Adjusted analyses (using ANCOVA) were also performed. Prior to carrying out the ANCOVA analysis the normality assumption was tested using a residual analysis and the residuals were checked to ensure that they are independent and have constant variance using a histogram of residuals and a plot of residuals against plotted values.

Empathy of practitioner

The CARE measure at 26 weeks was used to compare how the patients perceived the empathy of the practitioner they saw (in the IHT and

supportive listening arms), to see if there was any correlation between empathy of the practitioner and outcome for the patient.
It was intended that the relationship between empathy of practitioner and clinically significant change in IBS-SSS score was to be tested using logistic regression analysis. A change in IBS–SSS of ≥ 50 was defined as a responder, with the outcome being a clinically relevant change in IBS, and the predictors being CARE score and baseline IBS-SSS. It was thought likely that those with a higher initial IBS-SSS score were more likely to have a clinically relevant change than those with a lower initial score, hence it was proposed that initial IBS-SSS score would be included in the model.

7.1.8.2 Descriptive analyses

Health related quality of life
Health related quality of life was measured using the EQ-5D questionnaire 3L (3 level), measured at baseline and after 26 weeks. There are two types of the EQ-5D questionnaire, the 3L and the 5L, both ask the same questions. The difference being the 3L has 3 possible classes/levels of severity for each question whilst the 5L has 5 possible levels of severity. EQ-5D results were presented at both time points as the proportion of reported problems for each level for each dimension as recommended by the EuroQol group (EuroQol Group 2011). EQ-5D VAS was presented as mean and standard deviation for each time point unless the data was skewed, in which case they were presented as median values along with 25^{th} and 75^{th} percentiles, again as recommended by the EuroQol group (EuroQol Group 2011). Permission was sought to use the EQ-5D, which was granted without incurring any costs. This was because of the small scale of this study and the fact that it was not being carried out by a pharmaceutical company or any other profit-making stake-holder (see Appendix 8).
No statistical tests were carried on the EQ-5D data and exposure to treatment data due to concerns about multiple testing. The issue with multiple testing or multiple comparisons is that the more attributes that are compared the more likely it is that a difference will be found in at least one of the attributes. Most tests are carried out to the 95% confidence level i.e. 1 time in 20 a difference will be found when there is not really a difference, so the more tests that are carried out the more chance there is that a difference will be found when there isn't really a difference. Therefore the confidence in results where multiple comparisons have been carried out should be weaker. A solution to this problem is through the use of a correcting factor to correct

for the multiple comparisons, an example of this is the Bonferroni correction (Bland and Altman 1995). However the Bonferroni correction is rather conservative (Petrie and Sabin 2005). For this reason it was decided that in this study statistical tests would only be used to compare the primary outcome and HADS. This is because IBS-SSS, the primary outcome measure, is measuring the severity of the persons IBS-SSS, which is the main area of interest to this study. HADS was chosen because more people with IBS suffer with stress and anxiety than in the general population (Ten Berg *et al.* 2006) and an improvement in this may indicate a positive effect of treatment.

Exposure to treatment

The exposure to treatment of each of the two active treatment arms was measured through recording the number of appointments each patient attended. From this average number of IHT appointments and average number of supportive listening appointments attended were calculated and reported.

Credibility of treatment

Credibility of treatment was measured using a questionnaire developed by (Borkovec and Nau 1972) and adapted for IBS patients by (Drossman *et al.* 2003). This was measured after two appointments for IHT and supportive listening arms. From this the median credibility scores for IHT and supportive listening were compared.

Other comparisons

Comparisons of age, sex, IBS type and IBS-SSS score were made between those eligible for the RCT and randomly selected to IHT who took up the offer and those randomly selected to IHT who didn't take up the offer. This was to see if there are any differences between any of the characteristics of these people. No formal testing was carried out on this data, instead the information was tabulated and accompanied by a written narrative.

The same comparisons were carried out between those agreeing to supportive listening and those who declined it.

7.1.8.3 Missing data

There are three types of missing data, missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR)

(Little and Rubin 1987). MCAR means that there are no predictors as to why the data is missing, an example of this would be if a questionnaire had got lost in the post (Shih 2002). MAR is when the missingness depends on observed data and not on the unobserved data e.g. if there was a missing IBS-SSS score and the reason for it being missing depends on employment status of the participant (Sterne *et al.* 2009). MNAR is when the missing data is neither MCAR nor MAR i.e. the reasons for missingness depends on the missing observations (Sterne *et al.* 2009). An example of this would be where the IBS-SSS score is missing and the fact that the score is missing depends on the value of the score i.e. if a person had not returned their questionnaire because they had a high IBS-SSS.

To explore the reasons for missingness in this RCT the number of participants with missing data at 26 weeks was summarised along with reasons for missing data where available. For each outcome measure for each arm (IHT, supportive listening and usual care) the number of non-responders was calculated. The baseline characteristics for those with missing data were examined along with the reasons for missing data - where available. These were compared between the different arms. The aim was to assess whether the data was likely to be MCAR, MAR or MNAR. Missing data can be dealt with according to which type of missingness is present. In the case of MCAR then the fact that the data is missing will not have an impact on the overall result and a complete case analysis can be carried out (Shih 2002). If the data is MNAR, then a complete case analysis, along with a sensitivity analysis, where the missing data is inputted using multiple imputations, can be carried out and the results compared (Sterne *et al.* 2009). To determine whether the missing data in this study was likely to be MCAR, MAR or MNAR a logistic regression model was used to investigate whether missingness was associated with any demographic factors for IBS-SSS score and for HADS score (full details of this model are given in Chapter 9). If the data was found to be MCAR then a complete case analysis alone would be carried out, however if the data was MNAR, then the intention was for missing data to be inputted using multiple imputations (MICE) (Little and Rubin 1987) and the results compared between this and a complete case analysis.

7.2 Qualitative Interviews

As explained in Chapter 6, semi-structured in-depth interviews were conducted with participants in the IHT and supportive listening arms of the RCT. Interviews were also carried out with the therapists who provided the IHT and supportive listening. This section provides details of the methods used in these interviews, beginning with explaining how potential participants were identified and recruited.

7.2.1 Identification and Recruitment

Potential participants were sampled on completion of their 26 week BIBSC study questionnaire. Those identified as potential participants were at that stage only identifiable by the study number assigned to them as part of the BIBSC study. The principal investigator who had access to the document containing codes linking the BIBSC study numbers with names and addresses used this document to identify the names and addresses of potential participants. Once names and addresses had been identified, potential participants were sent an invitation letter along with a participant information sheet and consent form to sign and return. If they wished to take part they were asked to mail the researcher to arrange a convenient time for the interview to take place.

There were four therapists providing the treatments (two providing supportive listening and two providing IHT) in the RCT, all of whom were invited to take part in this study. The principal investigator had access to their names and contact details and sent them an invitation letter along with the participant information sheet and consent form to sign and return, copies of these are given in Appendix 9.

7.2.2 Study procedure

Participants were asked to take part in one interview which lasted one to one and a half hours. The focus of the interview was on the patient's or therapist's experience of the treatment they received or provided and what they found helpful or unhelpful about the treatment.

Interviews took place in the participant's homes or at another mutually convenient location. Funding was not available to cover participants travel expenses, and this was stated in the information sheet.

The interviews followed an in depth semi-structured format starting out broad and narrowing down to ensure that all the necessary topics had been covered by the end of the interview.

Two interviews were conducted initially as an internal pilot. The intention being to reflect on these and decide whether the topic guide required any modifications. Minor amendments to phrasing of questions would then be made as necessary prior to carrying out the remaining interviews. In the event it was decided that it was not necessary to change the topic guide.

Field notes were made whilst the interview was taking place or immediately after and interviews transcribed as soon as possible after they had taken place. Field notes contained a brief description of the setting for the interview along with a description of the participant and the main topics they raised, these were made as an aide-memoire.

7.2.3 Analysis

The qualitative data was analysed using framework analysis, the reasons why this methods of analysis was chosen are given in Chapter 6. Framework analysis consists of five key stages:

- Familiarisation, where the researcher familiarises themselves with the data through listening to the interviews and reading through transcripts. During this stage the researcher makes notes and jots down observations on recurrent themes and important issues.
- Identifying a thematic framework. In this stage the researcher identifies key issues, concepts and themes in the data, using the notes and observations they made during the familiarisation process.
- Indexing, in this stage the researcher applies the thematic framework to the data. Transcripts are read and coded according to the themes and concepts that were identified in the thematic framework.
- Charting. The indexed data is arranged into charts with headings and subheadings comprising of the themes identified in the thematic framework. It is important at this stage to ensure that the initial source of the data is clearly identifiable to allow it to be checked with the original source if required.
- Mapping and interpretation. Once all the data has been charted according to the core themes, key characteristics of the data are

explored. The researcher reviews, compares and contrasts the charts searching for patterns and connections, whilst at the same time seeking for explanation for these patterns within the data.

The results of this analytic process differ depending on the research question and the study aims, in this study the aim was to explore patients' and therapists' perceptions about IHT or supportive listening and provide an understanding of what people believed, if anything, was helpful about these treatments and what, if anything led to changes in IBS symptoms and overall health.

The exact details this analysis process are given in Chapter 10, which reports the results of the qualitative study. The reason the analysis is documented in detail in the results section rather than in the methods section is because the analysis involved an iterative process. In this process the results from the first stage of the analysis were used to inform the second stage of the analysis etc. Therefore knowledge of the results was needed in order to provide a detailed description of the analysis process, understandable to the reader.

In summary, this chapter has detailed the methods used in both the RCT and the nested qualitative study, providing information on how each of these studies was conducted. The next chapter will discuss ethical concerns associated with the RCT and qualitative study along with the potential for author bias when planning, conducting and analysing the work contained in this thesis.

8 Ethical Considerations

This chapter discusses the ethical considerations of both the RCT and the qualitative study, along with a section discussing the potential for author bias in this study.

Ethical approval for the formation of the Barnsley Irritable Bowel Syndrome Cohort (BIBSC) and the subsequent RCT was made in a single application to Leeds (East) Research Ethics Committee, reference 10/H1306/73. Ethical approval for the qualitative study was made to Leeds (Central) Research Ethics Committee, reference 11/YH/0178. See Appendix 10 for approval letters.

8.1 Ethical considerations in research

Research ethics are concerned with the planning, conduct and reporting of research. In research involving human participants, the researcher needs to ensure that the participants' moral and legal rights are protected (World Medical Association 2008). This involves ensuring that participants are fully informed about the possible risks and benefits of taking part in the research, enabling them to give consent having fully understood the implications of taking part. There should be no coercion in this process and the participants autonomy and privacy should be respected at all times (Royal College of Nursing Research Society 2011). Any risks associated with the research should be minimised, and participants should not be exposed to unacceptable risks. In addition to this, the research should be scientifically valid and have the potential to lead to an enhancement of knowledge or health (Emanuel, Wendler and Grady 2000). To ensure that this is the case the research protocol should be subject to independent review. In light of these requirements, the next section discusses the ethical concerns particular to the RCT study.

8.2 Ethical considerations in the RCT

The main ethical consideration for the RCT was the potential inclusion of the placebo tablet in the supportive listening arm. In particular there were difficulties around its inclusion without telling participants what it was. Other ethical considerations were:

- The ethics of conducting trials of homeopathy

- The informed consent process in trials using the Cohort Multiple RCT (cmRCT) model
- Adverse events
- Confidentiality and data storage

An application made to Leeds (East) Research Ethics Committee in September 2010 led to a number of concerns being identified by the research ethics committee's (REC), in particular:

- The ethics of carrying out a RCT investigation of homeopathic treatment
- Inclusion of a placebo tablet in the supportive listening arm of the RCT
- Informed consent in the cohort multiple RCT (cmRCT) model

These considerations, and the ways in which they were addressed, are now discussed.

8.2.1 The ethics of trials of homeopathy

The REC were unconvinced of the value of carrying out a trial of homeopathic treatment, stating: *"the committee felt that homeopathy is a placebo but if the researcher was clear about the issues around homeopathy then maybe it is ethically acceptable for a person to take part.*" They also said: "*the committee agreed the study could be approved if … the researcher explains that no clinical randomised trials have shown that homeopathy works*."

This feedback presented a dilemma as to what information to give participants about homeopathic treatment. As discussed in Chapter 4, there have been five meta-analyses of homeopathic treatment, four of which showed a favourable effect. The REC's conclusion that "no clinical randomised trials have shown homeopathy works" fails to take into account this evidence for homeopathic treatment. This, combined with the popularity of homeopathic treatment (Thomas, Coleman and Nicholl 2003), suggests that it is important that research continues to be carried out in an attempt to determine how homeopathic treatment differs from spending time with an empathetic practitioner.

Taking the above into account, and to meet the REC's requirements in terms of the information given to potential participants, the participant information sheet for the homeopathic treatment arm was amended by including the

following sentence. "*Homeopathic treatment involves a consultation with a homeopath followed by the prescription of a homeopathic remedy. It has been available on the NHS since 1948; however there is no clear proof as to whether or not it works. Whilst some patients report a benefit with homeopathic treatment we don't know whether this is the case for more than a handful of people. In this study we are trying to find out if homeopathic treatment improves IBS symptoms*".

It was considered that this sentence acknowledged the lack of clarity over the effectiveness of homeopathic treatment without deeming it ineffective, which could undermine participants' confidence in the treatment.

8.2.2 Inclusion of a placebo tablet

It was intended that the supportive listening arm of the trial would include a placebo tablet, as described in Chapter 6. However on submission of the protocol for the RCT to the REC, the REC asked what participants would be told if they asked what was in the placebo tablet. It was suggested that the placebo tablet would be called a milk sugar tablet (the base ingredient of homeopathic remedies). In a trial of hypnotherapy for non-cardiac chest pain (Jones *et al.* 2006), that had included a supportive listening plus placebo tablet arm, people had been told that the tablet was an anti-acid despite being a placebo (Whorwell 2010). However, due to changes in what participants can now be told in trials it had already been realised that it would be impossible to directly lie to participants about what the placebo tablet contained. Despite this the REC expressed concern that telling people that they were being given a milk sugar pill had the possibility of reducing any placebo effects as it would be apparent that this was an inactive tablet. Reducing the expectations of those in the "supportive listening plus placebo" arm could therefore potentially reduce the effect size for the supportive listening arm. The REC's suggestion was that the participants were told that they were being given a "dummy pill."

This suggestion was not considered desirable because it was highly likely to lead to a loss of credibility in the tablet. Indeed, some would consider it no longer to be a 'placebo' suggesting that a placebo only works because of what people *believe* that it is, or the meaning people attach to it (Moerman 2002). Following the logic of this REC, it would appear that there is a belief that placebos *per se* are unethical, as they fundamentally rest on deceiving patients in order to work. This is a belief that is based on the argument that placebos should not be used because they always require some kind of deception (Marusic 2004). However it could equally be said that it would not

be untruthful to say that a “placebo” may help, because it may indeed help, even if this is through the “placebo effect” rather than through any physiological means.

The REC’s comments provided an impetus to reflect on the role of the placebo tablet. The aim of including the placebo tablet was to control for the non-specific effects of being prescribed a medication. However without it the trial would be comparing two credible NHS treatments, supportive listening and IHT, against usual care. This led to the realisation that a decision had to be made as to whether the study should be looking at credible NHS treatments or answering explanatory questions.

In the scenario whereby two credible NHS treatments were compared the placebo tablet would be removed from the trial altogether and IHT and supportive listening for IBS would be compared. This would mean that the trial would be comparing two treatments that could potentially be obtained on the NHS and removed the issues around what to tell people about the placebo medication.

This scenario did also mean that those in the IHT arm received a tablet whilst those in the supportive listening arm did not, thus reducing the similarity in the treatment experiences. Nonetheless, without the placebo tablet it was considered that it would still be possible to determine whether IHT was better than giving a patient time and attention. Thus it was decided to remove the placebo tablet from the supportive listening arm.

8.2.3 Informed consent process in the Cohort Multiple RCT design

The intention was that potential participants in the Barnsley Irritable Bowel Syndrome Cohort (BIBSC) would be sent a participant information sheet explaining the purpose of the study along with an invitation letter and a questionnaire with a consent form on the back. It was made clear in the participant information sheet that a decision not to take part would in no way affect any of their current or future treatments. Those interested in taking part needed to complete and return the questionnaire and sign the consent form. Those randomly selected to be offered either supportive listening or homeopathic treatment would then be sent a participant information sheet containing details of the treatment they had been offered along with a further consent form to sign and return. It was made clear in the participant information sheets that a decision not to take part would not affect their inclusion in the BIBSC study.

In the cmRCT design people are not told about treatments they are not going to be offered, the reason being that telling people about treatments they are not being offered could lead to participant disillusionment (resentful demoralisation (Torgerson and Torgerson 2008)), if the participant does not get the treatment they wanted. This may then lead them to falsely report their outcomes, become uncooperative, non-compliant or even withdraw from the study, which could threaten the validity of their outcomes and thus introduce bias into the trial (Torgerson 1998). The rationale for the cmRCT is that it offers a more pragmatic approach whereby information and consent processes aim to mimic those undertaken in real world health care. This means that participants are only informed about the treatment they are being offered and not about other treatments that they have not been offered. Thus all participants in the cohort consent to provide observational data, whilst only those who are offered an active treatment consent (or not) to the treatment they have been offered.

To follow the cmRCT model, in this study participants who were randomly selected to the offer of a treatment were not going to be told that there was another treatment arm. However the REC stated that "*It must be clear that the cohort understands the nature of what will happen and that they may be offered interventions and explain what these interventions are.*"

To resolve this issue it was felt that there were three options for the way forward:

- Provide the REC with further rationale for the use of the cmRCT model.
- Explain in the participant information sheet for the BIBSC that there is a possibility that members of the BIBSC may be randomly selected to be offered a treatment.
- Carry out a standard RCT without the formation of a wider cohort (BIBSC).

Reflecting on these options and given the time constraints of the wider trial it was decided to go with the second option and explain at the outset that there was the possibility of members of the BIBSC being randomly selected to be offered a treatment.

It was noted that the same REC had previously approved a study that used the cmRCT model, however in that instance ethical approval for the formation of the cohort was applied for and granted first and then subsequently permission for each RCT trial using the cohort was applied for

separately. This suggests that a “staged” application for ethical approval may be more straightforward.

8.2.4 Adverse events

An adverse event is an unfavourable change in health that occurs either, whilst a patient taking part in a clinical trial that involves receiving a treatment, or within a pre-specified period of time after completion of the treatment. The procedure for dealing with any adverse events in the RCT was as follows. In the event of a patient reporting concerns to either the homeopaths or supportive listening providers they were advised to talk to their GP or consultant. The homeopaths and supportive listening providers enquired at each appointment whether the patient had experienced any unusual or unexpected events and any such events were recorded by the clinician. All patients remained under the care of their GP or hospital consultant.

8.2.5 Confidentiality and data storage

To ensure participant confidentiality all data was stored in accordance with data protection requirements made under The Data Protection Act (The National Archives 1998). This act requires that data be stored securely and for no longer than necessary. To this end all data was kept either in a locked filing cabinet in a secure office, or in the case of electronic data on a secure server with a password protected computer and files. No data was stored on a home computer or laptop.

On inclusion into the study participants were given a code. Codes and the corresponding names were kept in a separate document stored on a secure server and accessed by a password protected computer that only the research team had access to. Audio recordings of the supportive listening sessions were down-loaded onto a password protected computer and stored on a secure server and deleted from the recording device.

8.3 Ethical considerations for the qualitative study

The main ethical issues for the qualitative study were:

- The informed consent procedure
- Participants withdrawal and subsequent use of data
- Safety of participants and researcher
- Confidentiality and data storage

Each of these will be discussed in turn below.

8.3.1 Informed consent procedure

Potential participants were sent a participant information sheet explaining the purpose of the study along with an invitation letter and consent form. It was made clear in the participant information sheet that those who were not interested in taking part in the interviews were still able to remain in the BIBSC study and that a decision not to take part would in no way affect any of their current or future treatments. Those interested in taking part needed to mail, phone or e-mail to express their interest and arrange a convenient time for the interview to take place. When the potential participant made contact to arrange an appointment time there was the opportunity for them to ask any questions and seek further clarification about what the study would entail.

Signed consent forms were collected at the start of the interviews following discussion with the interviewer.

8.3.2 Participant withdrawal and subsequent use of data

Participants were informed of their right to withdraw at any time and without giving a reason. This was explained in the participant information sheet and reiterated prior to starting the interview.

If a participant chose to withdraw during the interview process they were asked whether they consented to have any data already collected being included in the study. If they did not agree to this, all data collected during the interview was destroyed. However if they consented to the data already collected being included, the data collected up to the point of withdrawal was included in the study.

8.3.3 Assessment of Safety

Participants

a) Patients

There was a slight risk that patients may find talking about their treatment distressing. In order to minimise this, and to help to make sure that patients were prepared for the interview, an outline of areas that the interviews would cover was provided in the participant information sheet.
If a participant became distressed during the interview, the interview was stopped and the interviewer asked the participant if they wanted to continue. If the answer was yes, the interviewer took a short break before continuing. If the answer was no, the interview was stopped at that point and the

participant thanked for their participation. Assistance was given to help the participant identify appropriate sources of support, or if necessary a recommendation made that they contact their GP.

b) Therapists

There was a slight risk that the therapist may feel uncomfortable talking about the treatment they provided. However the therapists had all expressed an interest in providing feedback about the RCT and talking about participants' reaction to the treatment they received, so it was felt that this was unlikely. However an outline of the areas that the interview would cover was provided in the participant information sheet, in order to ensure that the therapists were prepared for the interview.

Researcher

The researcher was travelling alone and conducting interviews in the participants' homes. To ensure the researcher's safety at all times the University's lone worker policy was followed and a risk assessment completed. This covered information such as providing a third party with details of the interview times and locations and procedures for getting help in the unlikely event of a problem arising during an interview.

8.3.4 Confidentiality and data storage

All data was stored in accordance with data protection requirements and was kept either in a locked filing cabinet in a secure office or in the case of electronic data on a secure sever with a password protected computer and files.

Participants' names and contact details were stored in a locked office and only accessed by the research team. Electronic (anonymised) data was stored on password-protected secure computers in the research team members' locked offices.

Audio recordings of the interviews were downloaded onto a password protected computer and deleted from the recording device.

All data will be stored for two years after completion of the PhD viva, which will allow time for any academic challenge to be made. All data will be deleted after this time.

On inclusion in the study participants were given a code. Codes and the corresponding names were kept in a separate document stored on a secure server and accessed by a password protected computer that only the research team had access to.

Any quotations used in the final report or any other publications were anonymised through giving the participants a pseudonyms.

Any comments made by the participants about the therapists were anonymised to ensure that it was not possible for individuals to be identified by the therapists.

8.4 Author bias

The author of this thesis is a professional homeopath and a member of the Society of Homeopaths. As such there is a potential for the author to be biased in terms of a desire to find homeopathy to be effective. Part of the homeopathic training involves learning, as far as it is possible, to take the stance of the unprejudiced observer (Kent 1984). This means acknowledging that it is impossible not to have any prejudices, but that through being aware of one's prejudices it is possible to question one's self and one's thoughts and actions. The author has attempted to do this throughout this study, by questioning decisions made, and reflecting whether or not they have been made as a result of a prejudiced stance.

Another way in which bias was minimised was the writing of an analysis plan for the RCT prior to conducting any analysis of the data. This was to ensure that results were not based on post hoc analyses that were designed to show homeopathic treatment in the best light possible. In addition a statistician was consulted throughout, with regard to both the analysis plan and subsequent analysis. As a further quality control check, the protocol for the study was peer reviewed by two independent reviewers prior to submission to the REC.

One of the funders of this study, the Homeopathy Research Institute (HRI), is a charity that provides funding for homeopathy research. This could have introduced a potential conflict of interest had they been involved in the design, analysis, writing or dissemination of the study results. However the HRI solely provided part of the funding for this study and had no involvement in the writing of the analysis plan, subsequent analysis and conduct of the study. Funding was given prior to the research commencing and not on the production of a positive result.

In summary, this chapter has briefly explored the principles governing research ethics before moving on to discuss the ethical concerns relating to the RCT and qualitative study. In particular it explains why it was decided not

to include a placebo tablet in the supportive listening arm and the REC's concerns about trials of homeopathic treatment.

The results of the RCT are discussed in the next chapter.

9 Results

This chapter reports the results from the RCT. The analysis of the results was conducted as per the analysis plan described in Chapter 7.

9.1 Recruitment

Between January 2011 and June 2011, 596 people, from four GP surgeries and one secondary care unit, were sent a questionnaire and an invitation to take part in the Barnsley Irritable Bowel Syndrome Cohort Study (BIBSC). Of these, 154 people returned questionnaires, 115 of whom met the eligibility criteria for the BIBSC. Those eligible for the BIBSC were screened for eligibility for the RCT. 94 people met all the RCT inclusion criteria and none of the exclusion criteria. The Consolidated Standards of Reporting Trials (CONSORT) diagram (Schulz *et al.* 2010), Figure 9-1 shows the flow of participants through the recruitment process. The overall response rate was 26% (154/596) with 19% (113/596) of those sent a questionnaire being eligible to take part in the BIBSC study and 16% (94/596) being eligible to take part in the RCT.

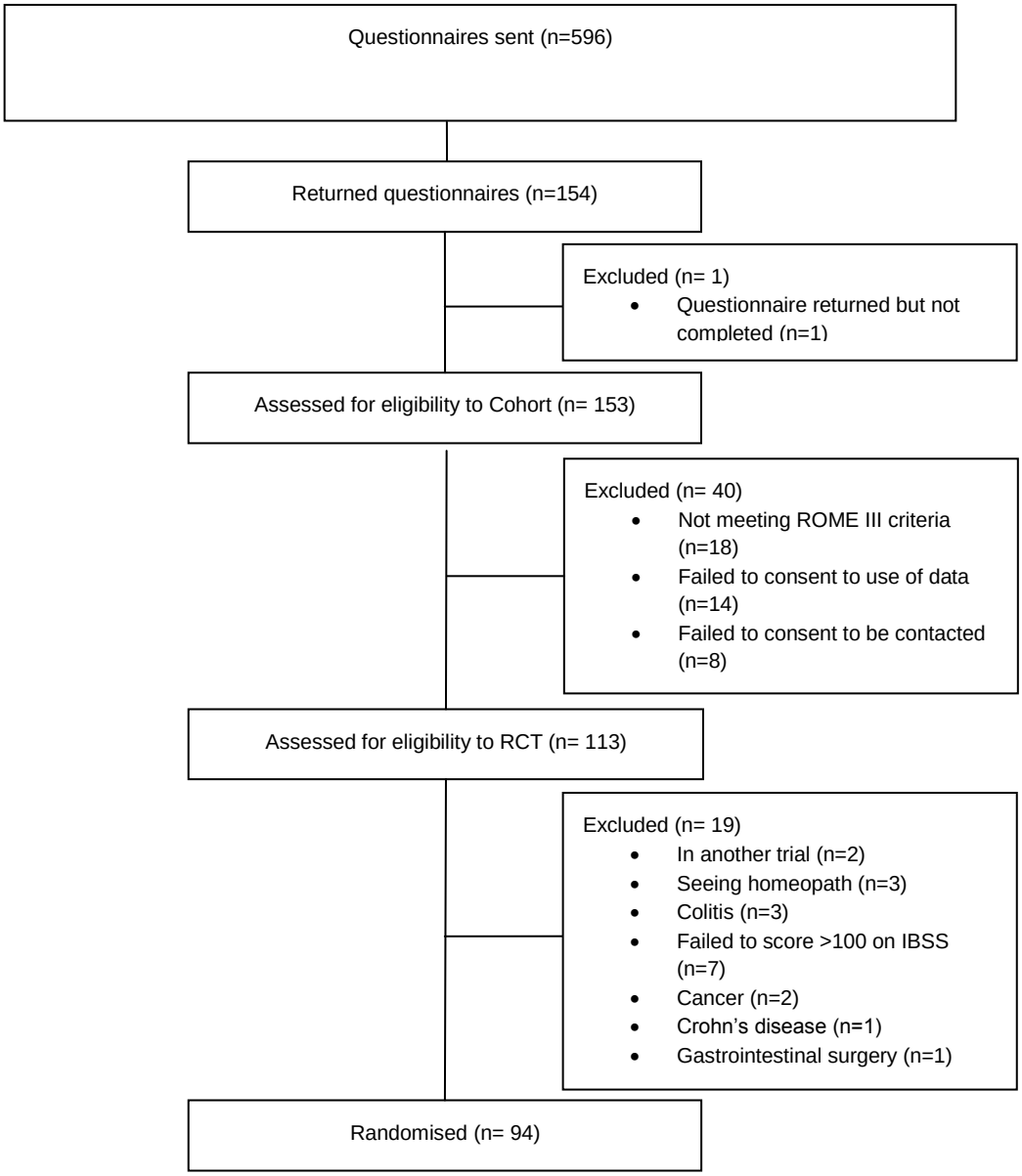

Figure 9-1: CONSORT diagram for recruitment

9.1.1 Randomisation

A total of 94 people were randomised and allocated to usual care (n=60), IHT plus usual care (n=16) or supportive listening plus usual care (n=18). Of these 12/18 (75%) took up the offer of IHT and 9/18 (50%) took up the offer of supportive listening. Where possible the reasons for not taking up the offer of treatment were sought, however this was not always possible. Reasons given included: too many other appointments, poor health, unable to take time off from caring duties, being deaf and happy to live with IBS.

One person cited each of the reasons listed. Full details of the randomisation process are reported in the randomisation CONSORT diagram (Figure 9-2).

A record of mailing dates for the initial questionnaires was kept, which allowed participants to be mailed a 26 week questionnaire exactly 26 weeks after they were mailed the initial questionnaire.

IBS-SSS data was collected at 26 weeks for 85 of the 94 people randomised. Those who did not return their 26 week questionnaire were contacted by telephone and asked if they would answer questions from the IBS-SSS over the telephone. Table 9-1 gives a summary of questionnaire returns for each arm. Those who did not complete their 26 week questionnaire and were unable to be contacted by telephone have been defined as lost to follow up at 26 weeks, with 9 people being lost to follow up. The percentage in brackets refers to the percentage of total people recruited that were allocated to each intervention.

	Usual care N=60 (64%)	IHT N=16 (17%)	Supportive listening N=18 (19%)
Number randomised	60	16	18
Number who took up offer of treatment	N/a	12	9
Withdrawn from trial prior to treatment	0	0	0
Withdrawn from trial treatment	0	0	0
Completed 26 week questionnaire	51	15	11
Contacted by phone for IBS-SSS	3	1	4
Total who gave IBS-SSS	54	16	15
Loss to follow up 26 weeks	6	0	3

Table 9-1: Summary of participant flow

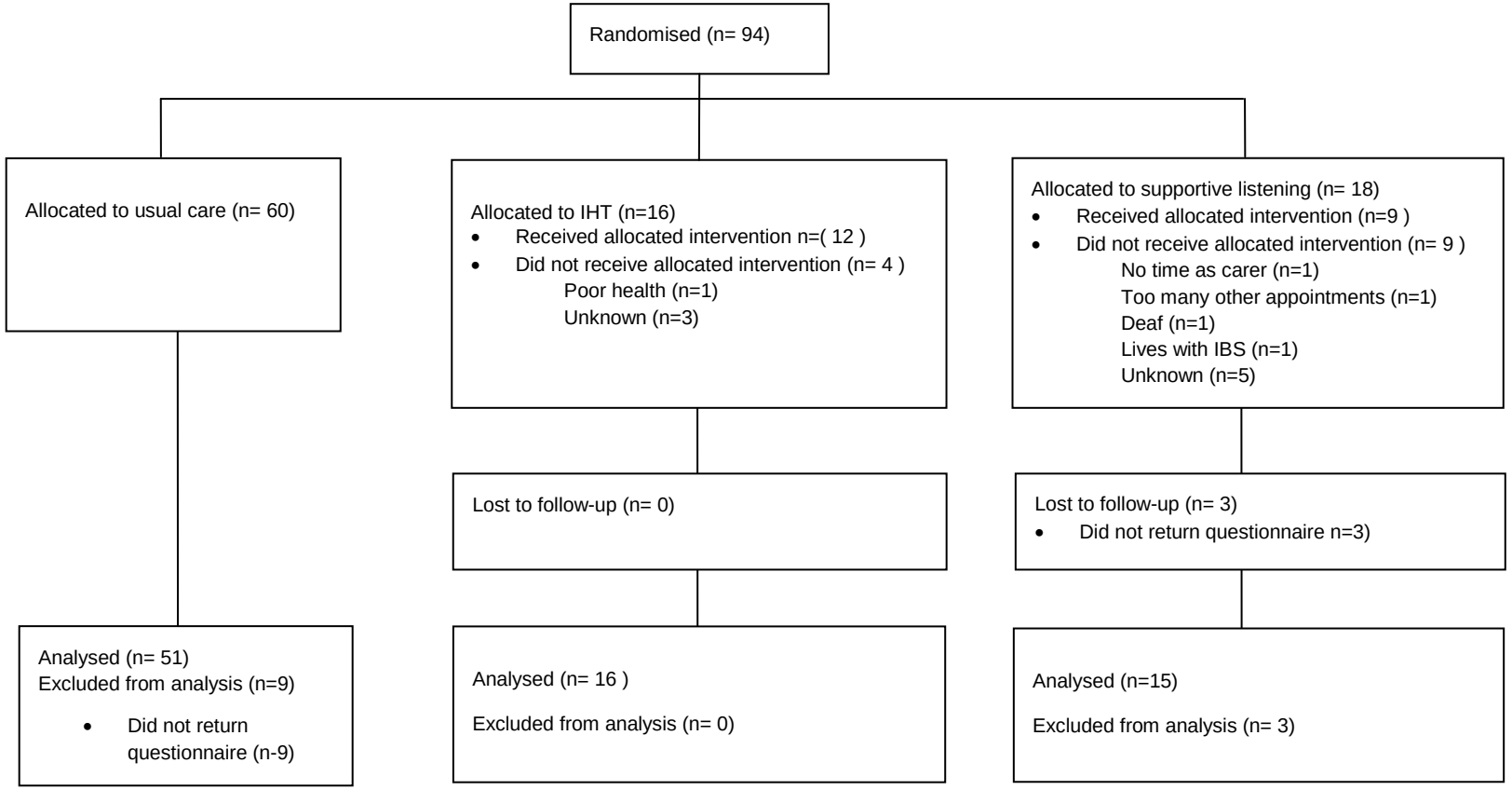

Figure 9-2: CONSORT diagram of the randomisation process

All of those recruited lived in the Barnsley area and described themselves as of white British origin. The mean age of participants was 49 (standard deviation 14.70). The majority (83%) of the participants were female. Most (53%) of the participants were employed. The remainder were either not employed (44%) or did not provide this information (3%). Table 9-2 gives details of the baseline characteristics of the participants in each arm of the trial.

		Usual Care N=60	IHT N=16	Supportive listening N=18
Gender	Male	12 (20%)	0 (0%)	4 (22%)
	Female	48 (80%)	16 (100%)	14 (78%)
Age	Mean (sd)	51.71 (14.20)	48.19 (13.45)	42.50 (16.17)
	Missing	2	0	2
Employment	Employed	28 (46.7%)	11 (68.8%)	11 (61.1%)
	Unemployed	31 (51.7%)	5 (31.3%)	5 (27.8%)
	Unknown	1	0	2
Number of prescribed medicines	Mean (sd)	4.60 (4.18)	2.56 (2.31)	2.94 (2.71)
	Missing	0	0	0
IBS-SSS	Mean (sd)	250.87 (78.60)	280.38 (79.43)	291.61 (74.38)
	Median (IQR)	243.50 (188.00-324.00)	275.00 (205.00-344.25)	289.50 (224.75-340.00)
	Missing	0	0	0
HADS-D	Mean (sd)	5.82 (3.69)	5.88 (4.54)	6.94 (4.91)
	Median (IQR)	6.00 (2.25-8.00)	3.50 (3.00-9.50)	6.00 (2.75-10.25)
	Missing	0	0	0
HADS-A	Mean (sd)	10.13 (4.74)	11.13 (4.49)	10.11 (4.80)
	Median (IQR)	10.00 (6.25-14.00)	10.50 (7.50-15.25)	11.50 (6.50-14.00)
	Missing	0	0	0
EQ-5D Global	Mean (sd)	58.25 (25.39)	59.00 (15.64)	62.57 (23.46)

Table 9-2: Baseline patient characteristics

It can be seen from the baseline characteristics that there were fewer men in the IHT arm (n=0, 0%) compared to the supportive listening (n= 4, 22%) and usual care arms (n=12, 20%). The initial mean IBS-SSS was lower for those in the usual care arm (250.87) compared to those in the IHT arm (280.38) and supportive listening arm (291.61). However the mean IBS-SSS for each

of the arms all lie within the confidence intervals for the other arms, i.e. the mean IBS-SSS for the usual care arm is 250 and the confidence intervals for the mean IBS-SSS for the IHT and supportive listening arms are 205.00 to 344.25 and 224.75 to 340.00 respectively. Formal testing of 'comparability' was not undertaken as this has low power to detect differences in samples formed in randomised trials and any imbalances (which will, be definition, have occurred by chance) will be accounted for in the analysis.

9.1.2 Care providers

Two homeopaths and two counsellors provided IHT and supportive listening respectively, at Barnsley Hospital NHS Foundation Trust. Table 9-3 shows the number of participants treated by each care provider.

Care provider	Number of participants randomized	Number of participants treated
Homeopath 1	10	8
Homeopath 2	6	4
Listener 1	14	7
Listener 2	4	2

Table 9-3: Number of participants treated by each care provider

Both of the homeopaths are registered with the Society of Homeopaths and have over five years clinical experience. Both of the listeners are qualified counsellors, registered with the British Association for Counselling & Psychotherapy and have over five years clinical experience.

9.1.3 Adherence to treatment

Whilst none of those in the treatment arms of the trial asked to withdraw from the trial, not all the participants attended all of the 5 treatment sessions that they were offered. Table 9-4 shows how many sessions people attended in each arm of the trial.

Number of sessions attended	IHT (n=16)	Supportive listening (n=18)
0	4	9
1	0	0
2	0	0
3	0	2
4	0	2
5	12	5

Table 9-4: Number of appointments attended

9.1.4 Adverse effects

No adverse effects were reported. However one participant in the IHT arm suffered an allergic reaction and sought medical attention, the reaction was not thought, by the doctor the participant consulted, to be due to the IHT.

9.1.5 Outcome Data

Table 9-5 gives details of participants in each of the three arms at 26 weeks. The higher IBS-SSS the more severe the IBS. All calculations are based on an intention to treat analysis unless otherwise stated.

		Usual care N=60	IHT N=16	Supportive listening N=18
Number of appointments	Mean (sd)	Not applicable	3.75 (2.24)	2.17 (2.31)
IBS-SSS 26 weeks	Mean(sd)	237.3 (110.22)	210.44 (112.40)	262.0 (120.72)
	Median(IQR)	221.0 (164.50-325.00)	180.0 (146.25-274.00)	235.0 (184.00-380.00)
	Missing	7	0	3
Change in IBS-SSS 26 weeks	Mean (sd)	-10.5 (78.770	-69.9 (114.75)	-45.7 (87.56)
	Median (IQR)	6 (-64-41.00)	-57.5 (-200-6)	-38.0 (-128-33)
	Missing	7	0	3
HADS 26 weeks	Mean(sd)	13.9 (7.37)	17.27 (6.28)	15.3 (8.52)
	Median(IQR)	13.0 (9-18)	15.0 (13-23)	13 (8-23)
	Missing	9	1	7
Change in HADS 26 weeks	Mean (sd)	-1.78 (4.64)	-0.2 (7,57)	-0.18 (4.75)
	median(IQR)	-2.0 (-5-2)	0.0 (-2-3)	2 (-5-3)
	Missing	9	1	7
CARE score	Mean		43.0 (10.48)	44.50 (3.87)
	Median (IQR)		50.0 (33.00-50.00)	43.50 (41.50-48.50)
	Missing*		3	5
Therapeutic rationale	Mean logical		5.83 (2.55)	4.00 (1.73)
	effective		5.5 (2.65)	5.00 (1.58)
	Median (IQR) logical		3.00 (3.00-5.50)	6.00 (5.00-7.75)
	effective		5.00 (3.50-6.50)	6.00 (5.00-7.00)
	Missing*		2	4

Table 9-5: Patient characteristics at 26 weeks

*This is the number of participants who attended at least two appointments but did not return their therapeutic rationale form. Those who declined the offer of treatment are not included in this number.

The outcomes for the EQ-5D dimensions were dichotomised into those that reported problems and those who did not report any problems. Dichotomising the dimensions in this manner is one of the ways that results from the EQ-5D dimensions can be reported as per instructions in the EQ-5D manual (EuroQol Group, 2011) (Cheung 2009). In the EQ-5D 3L (the version used in this trial) participants have the option of ticking one of three boxes for each of the dimensions. Table 9-6 shows the options for the mobility dimension. In the case of the mobility dimension those that ticked the top box would be defined as having no problems and those that ticked either the middle or bottom box would be defined as having problems. The same applied for the other 4 dimensions.

Mobility	**Please tick one**
I have no problems in walking about	
I have some problems in walking about	
I am confined to bed	

Table 9-6: EQ-5D mobility dimension

Table 9-7 gives details of the number of people who reported problems for each of the EQ-5D dimensions, at baseline and 26 weeks.

EQ-5D dimension		Usual care		IHT		Supportive listening	
		Before	After	Before	After	Before	After
Mobility	No problems	45	37	10	12	15	7
	Problems	15	13	5	3	3	3
	Missing	0	8	1	1	0	4
Self care	No problems	50	44	15	15	18	9
	Problems	9	16	0	0	0	1
	Missing	1	8	1	1	1	4
Usual activities	No problems	35	30	11	9	13	7
	Problems	25	20	5	6	5	3
	Missing	0	8	0	1	0	4
Pain/	No problems	9	6	0	2	5	1
discomfort	Problems	50	44	16	12	13	10
	Missing	1	8	0	2	0	3
Anxiety/	No problems	24	22	6	4	11	4
Depression	Problems	36	27	10	11	7	6
	Missing	0	9	0	1	0	4
EQ-5D VAS	Mean (sd)	62.57 (23.46)	63.41 (23.31)	59 (15.64)	69.07 (17.35)	58.25 (23.39)	63.09 (24.38)
	Median (IQR)	68.0 (47-82)	69 (46-80)	60 (50-70)	72.5 (61-81)	63.5 (39-80)	70 (40-85)
	Missing	2	7	1	2	7	9

Table 9-7: EQ-5D scores before and after treatment

Following dichotomisation the percentage of participants who reported problems was calculated for each dimension (mobility, self care, quality of life, pain and anxiety and depression), for each arm of the trial, both at baseline and after 26 weeks.

For clarity and to follow the two pre-specified comparisons, the percentage of patients who reported problems in the usual care arm (UC) compared to those in the IHT arm (HT) (Figure 9-3) and the percentage of patients who reported problems in the IHT arm (HT) compared to those in the supportive listening arm (SL) (Figure 9-4).

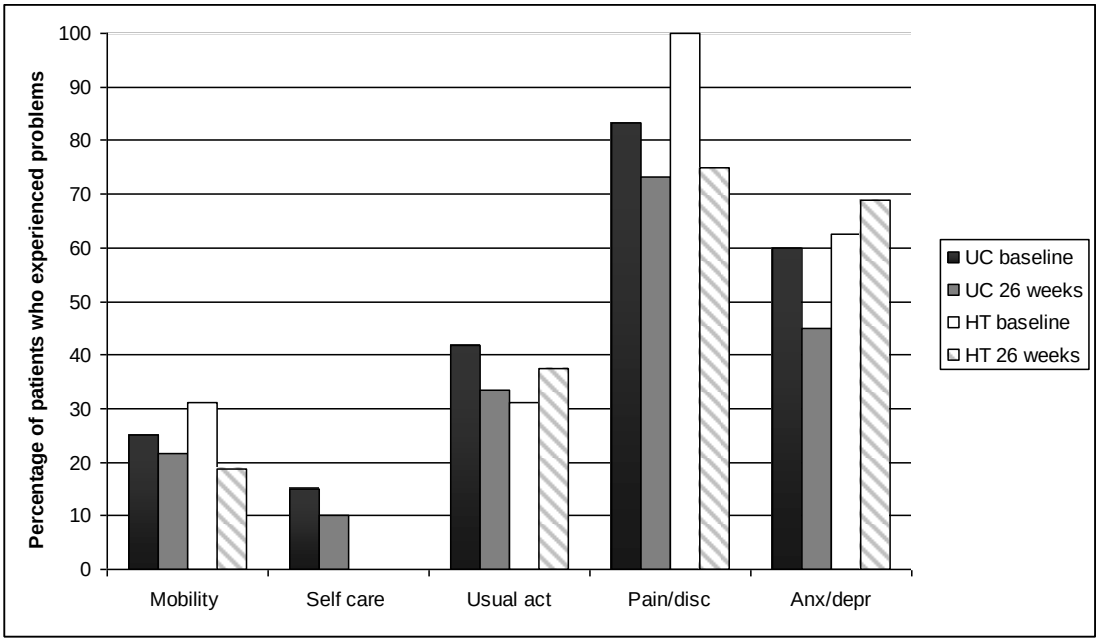

Figure 9-3:EQ-5D dimensions of usual care arm compared to IHT arm

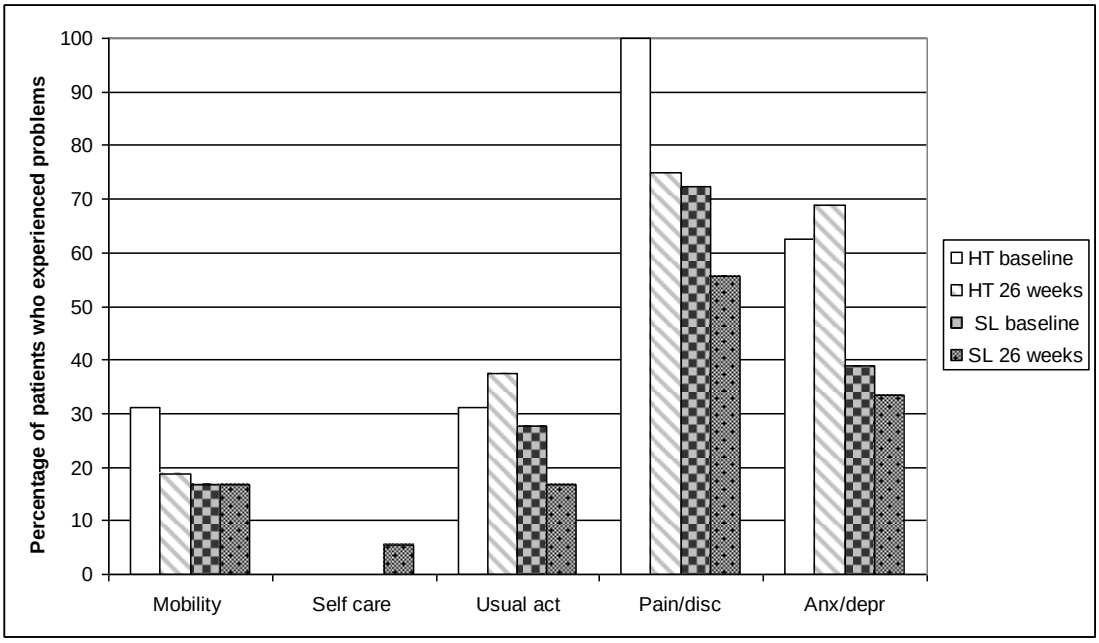

Figure 9-4: EQ-5D dimensions of IHT compared to supportive listening

9.1.6 Missing data

Participants were sent a 26 week questionnaire and one reminder. Participants who did not return their 26 week questionnaire were contacted by telephone and asked if they would give their 26 week IBS-SSS over the telephone. Table 9-8 gives details of return rates for the 26 week questionnaires and phone IBS-SSS. Details are given as n/N where n is the

number of people who performed that action and N is the total number of people in that arm of the trial.

	Returned 26 week questionnaire	Phone IBS-SSS given	No 26 week data
Usual care	51/60 (85%)	3/60 (5%)	6/60 (10%)
IHT	15/16 (93.75%)	1/16 (6.25%)	0/16 (0%)
Supportive listening	11/18 (61.11%)	4/18 (22.22%)	3/18 (16.67%)

Table 9-8: Return rates for the 26 week questionnaire

As explained in Chapter 7, there are three types of missing data, missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR).

Missing 26 week IBS-SSS

To assess whether it is likely that the missing 26 week IBS-SSS is MCAR, MAR or MNAR a comparison of baseline data was made between those who didn't return their 26 week IBS-SSS and those who did. The data on those who didn't return their 26 week questionnaire includes those whose IBS-SSS was sought by telephone but who didn't return their 26 week questionnaire. Table 9-9 gives these comparisons. Comparisons between those who returned their 26 week IBS-SSS and those who did not return their 26 week IBS-SSS were also made for the usual care and supportive listening arms, everyone in the IHT arm returned their 26 week IBS-SSS. This was to see if there were any differences between the arms of the trial.

		Across all arms			Usual care		Supportive listening	
		Did return (N=85)	Did not return (N=9)	P	Did return (N=54)	Did not return (N=6)	Did return (N=15)	Did not return (n=3)
Sex	% female	82.1	90.0	0.532	72.2	85.7	73.3	100
	Missing	0	0		0	0	0	0
Age	Mean	50.64 (13.87)	38.67 (18.28)	0.02	53.04 (13.00)	42 (19.55)	44.71 (16.03)	27.00 (5.66)
	Missing	3	1		2	0	0	1
IBS-SSS	Mean	264.64 (82.18)	255.70 (47.60)	0.617	247.72 (81.90)	274.71 (43.30)	307.67 (70.79)	211.33 (18.77)
	Median	254.00 (189.25–336.75)	248.00 (214.75–306.75)		243.00 (181.00-326.50)	262.00 (237.00-318.00)	313.00 (267.00-434.00)	215.00
	Missing	0	0		0	0	0	0
EQ-5D	Mean	61.88 (22.63)	55.40 (21.80)	0.396	63.13 (23.69)	58.86 (23.33)	60.77 (26.61)	47.33 (19.14)
	Median	67.50 (49.75-80.00)	62.50 (38.25-72.50)		68.50 (48.00-84.25)	65.00(42.00-80.00)	70.00 (42.00-82.00)	50
	Missing	10	0		7	0	2	0
Employed	% employed	51.2	77.8	0.147	43.4	71.4	64.3	66.7
	Missing	2	1		1	0	1	1
HADS	Mean	16.60 (7.73)	14.2 (7.28)	0.354	16.15 (7.39)	14.43 (8.04)	17.73 (9.14)	13.67 (6.66)
	Median	16.00 (11.00-22.50)	13.50 (8.25-19.25)		17.00 (11.00-22.00)	10.00 (9.00-23.00)	16.00 (11.00-24.00)	6
	Missing	0	0		0	0		

Table 9-9: Baseline comparisons between those who did and did not return their 26 week IBS-SSS

It can be seen that those who returned their 26 week IBS-SSS were older (mean age 51) than those who did not (mean age 38) and were more likely to be employed (51.2%) than those who did not (77.8%).

Student's T-tests were used to calculate p values for the differences in age, IBS-SSS, EQ-5D and HADS between those who did and those who did not

return their 26 week IBS-SSS. Pearson's chi-square test was used to determine if the differences between those who did and did not return their IBS-SSS in terms of employment status and gender were statistically significant. From these tests only age ($p=0.02$) was found to be statistically significant ($p<0.05$). Therefore age appears to be related to whether participants returned their 26 week IBS-SSS. Younger people were less likely to return the questionnaire.

In the usual care arm it can also be seen that fewer of those who returned their 26 week questionnaires were employed, 43.4% compared to 71.4% of those who didn't return their score. This difference was smaller in the supportive listening arm with 64.3% of those who returned their 26 week IBS-SSS being employed compared to 66.7% of those who didn't return their score. Those in the supportive listening arm who did not return their 26 week IBS-SSS were younger (mean age 27) than those who did (mean age 45), this was also true for the usual care arm, with the mean age of those who did not return their 26 week IBS-SSS being 42 and the mean age of those who did return their 26 week IBS-SSS being 53.

These comparisons show that there appears to be a correlation between missing IBS-SSS and age. This means that it unlikely that the data in MCAR.

A higher percentage of those in the supportive listening arm (20%) did not return their 26 week IBS-SSS compared to those in the IHT (0%) and usual care arms (13%). Pearson's chi-square test was used to determine if the differences in the response rate were statistically significant. Table 9-10 shows the cross tabulation of missing 26 week IBS-SSS and allocation. Table 9-11 shows the results for Pearson's chi-square. It can be seen that the p value was 0.265; therefore there is no evidence of a correlation between allocation and missing 26 week IBS-SSS.

		26 week IBS-SSS not missing	26 week IBS-SSS missing	Total
Allocation	usual care	53	7	60
	IHT	16	0	16
	Supportive listening	15	3	18
Total		84	10	94

Table 9-10: Cross tabulation of missing 26 week IBS-SSS by allocation

	Value	Df	p
Pearson Chi-square	2.66	2	0.27

Table 9-11: Pearson's Chi-square for missing IBS-SSS by allocation

A logistic regression model was also carried out to determine if any of the factors that may have affected missingness of data were significant for IBS-SSS.

A logistic regression model was set up with 26 week IBS-SSS as the dependent variable. This is a binary variable as it the data is either missing or not, in this model missing 26 week IBS-SSS was coded as 1 and not missing IBS-SSS was coded as 0. Covariates chosen as possible predictors of missingness were: age and IBS-SSS as continuous variables, and employment and allocation as categorical variables. These were chosen because in the above comparisons there are appeared to be some differences between the employment status and age of responders and non-responders. As already reported, there was a difference between the percentage of people in the supportive listening arm who returned their IBS-SSS and the percentage of people in the IHT arm, hence allocation was included in the model. Finally initial IBS-SSS was chosen as it was thought possible that returning 26 week IBS-SSS may be related to initial IBS-SSS. It should be noted that the number of events (i.e. number of missing data points) for IBS-SSS was only 10. Therefore following the rule of 1 predictor per 10 events only 1 allows for 1 predictor to be included in the regression equation (Peduzzi *et al.* 1996). This means that the results of the regression should be viewed with caution. However the regression was carried to determine whether it backed up the results obtained from the comparisons made above. The results from the regression are shown in Table 9-12.

Predictor	B	SE β	Wald's x^2	df	P	e^{β} odds ratio
Constant	0.875	2.269	0.149	1	0.700	2.399
Age	-0.060	0.031	3.740	1	0.053	0.942
Employment (employed = 1, not employed =0)	0.590	0.919	0.412	1	0.521	1.805
IBS-SSS	-0.003	0.005	0.473	1	0.492	0.997
Allocation			0.232	2	0.890	
Allocation (1) usual care =1	0.458	0.950	0.232	1	0.630	1.581
Allocation (2) IHT = 1	-18.986	9552.556	0.000	1	0.998	0.000

Table 9-12: Regression model for missing 26 week IBS-SSS

None of the p values in this model were less than 0.05, therefore the regression model indicated that none of: employment status, sex, age and baseline IBS-SSS were significant predictors to missing IBS-SSS in this small study. The Cox and Snell pseudo r^2 was 0.113 which indicates that the model does not provide a good explanation as to why the data is missing. This may be due, in part, to the low event rate for this data, meaning that these results should be viewed with caution as there may be insufficient power to detect predictors.

From the results obtained from the comparisons between missing IBS-SSS and baseline data and the regression it can be seen that there is a potential correlation between missing 26 week IBS-SSS and age. In terms of dealing with this missing data it is believed that the data is not MCAR. However the missingness is not substantial. A statistician was consulted for advice as to how to deal with the missing data and it was advised that if the variables associated with missingness are included in an ANCOVA then this will balance the analysis. Hence in the ANCOVA model for the primary outcome age and employment status will be included.

Missing 26 week HADS

To assess whether it is likely that the missing data for 26 week HADS is MCAR, MAR or MNAR a comparison of baseline data was made between those who didn't return their 26 week HADS and those who did, Table 9-13.

		Across all arms			Usual care		IHT		Supportive listening	
		Did return (N=77)	Did not return (N=17)	P	Did return (N=51)	Did not return (N=9)	Did return (N=15)	Did not return (N=1)	Did return (N=11)	Did not return (n=7)
Sex	% female	83.1	82.4	0.940	80.4	77.8	100	0	72.7	85.7
	Missing	0	0		0	0	0	0	0	0
Age	Mean	52.07 (13.95)	37.31 (11.97)	0.00	54.18(13.18)	38.22 (12.38)	47.93 (13.89)	52.00	47.90 (16.78)	33.50 (11.06)
	Missing	3	1		2	0	0	0	1	1
IBS-SSS	Mean	259.77 (80.20)	281.47 (73.38)	0.308	246.08 (80.82)	278.00 (61.39)	280.73 (82.21)	275	294.64 (61.77)	286.86 (96.30)
	Median	248.00 (188.00-328.50)	267.00 (221.50-328.50)		243.00 (176.00-326.00)	262.00 (225.50-334.50)	275.00 (198.00-351.00)	275	313 (265.00-343.00)	267.00 (215.00-339.00)
	Missing	0	0		0		0	0	0	0
EQ-5D	Mean	62.10 (22.31)	57.18 (23.51)	0.423	62.66 (24.00)	62.00 (21.97)	59.64 (16.02)	50	63.22 (24.09)	51.86 (27.43)
	Median	60.00 (49.00-80.00)	62.00 (46.00-77.50)		68.50 (46.00-84.00)	65.00 (51.00-80.00)	62.00 (50.00-70.25)	50	70.00 (42.00-84.50)	62.00 (27.00-75.00)
	Missing	10	0		7		1	0	2	0
Employed	% employed	45.5	88.2	0.00	39.2	88.9	66.7	100	45.5	85.7
	Missing	2	1		1	0	0	0	1	1
HADS	Mean	16.04(7.71)	17.71 (7.67)	0.421	15.75 (7.49)	17.11 (7.27)	17.47 (7.90)	10	15.45 (8.91)	19.57 (8.48)
	Median	15.00 (10.50-21.00)	18.00 (10.00-23.00)		16.00 (10.00-21.00)	18 (9.5-23.00)	15.00 (12.00-24.00)	10	15.00 (10.00-21.00)	18.00 (16.00-28.00)
	Missing	0	0		0	0	0	0	0	0

Table 9-13: Comparison of baseline data between those who did and did not return their 26 week HADS

It can be seen from that those who returned their 26 week HADS were older (mean age 52), than those who did not (mean age 37) and fewer of those who returned their 26 week HADS were employed (45.5%), compared to 88.2% of those who did not return their score. A Student's t-test was used to calculate a p value for the differences in age and ($p<0.01$) was found to be statistically significant. Pearson's chi-square test was used to determine if employment status was a significant predictor of failing to return 26 week HADS. The p value ($p<0.01$) indicated that employment status was a statistically significant predictor. Therefore age and employment status are related to whether participants returned their 26 week HADS.
In the usual care arm it can also be seen that fewer of those that returned their 26 week HADS were employed (39.2%) compared to 88.9% of those who didn't return their score. The same was observed in the supportive listening arm with 45.5% of those who returned their 26 week HADS being employed compared to 85.7% of those who did not return their score. Those in the supportive listening arm who did not return their 26 week HADS were younger (mean age 34), than those who did (mean age 48), this was also true for the usual care arm, with the mean age of those who did not return their 26 week HADS being 38, and the mean age of those who did return their 26 week HADS being 54.
These comparisons show that there appears to be a correlation between missing HADS and employment status and missing HADS and age. This means that it unlikely that the data in MCAR.

In terms of allocation, 17.65% of those in the usual care arm did not return their 26 week HADS, 6.67% of those in the IHT arm and 63.64% of those in the supportive listening arm. Pearson's chi-square test was carried out to determine if the difference in these results was statistically significant.

Table 9-14 shows the cross tabulation of missing 26 week IBS-SSS and allocation.

		26 week HADS not missing	26 week HADS missing	Total
Allocation	usual care	51	9	60
	IHT	15	1	16
	Supportive listening	11	7	18
Total		77	17	94

Table 9-14: Cross tabulation of missing 26 week HADS by allocation

Table 9-15 shows the results for Pearson's chi-square, it can be seen that the p value was 0.03, therefore there is a correlation between allocation and missing 26 week HADS.

	Value	df	P
Pearson Chi-square	7.16	2	0.03

Table 9-15: Pearson's Chi-square for missing HADS by allocation

A logistic regression model was also carried out to determine if any of the factors that may have affected missingness of data were significant for HADS. There were a greater number of people with missing 26 week HADS than there was for missing 26 week IBS-SSS. This is because only the 26 week IBS-SSS was sought over the telephone from those who did not return their 26 week questionnaire.

A logistic regression model was set up with 26 week HADS as the dependent variable. This is a binary variable, the data is either missing or not, in this model missing 26 week HADS was coded as 1 and not missing HADS was coded as 0. Covariates chosen as possible predictors of missingness were: age and IBS-SSS as continuous variables, and employment and allocation as categorical variables. These were chosen because in the above comparisons there are appeared to be differences between the employment status and age of responders and non-responders. As already reported, there was a difference between the percentage of people in the supportive listening arm who returned their HADS and the percentage of people in the IHT arm, hence allocation was included in the model. Finally initial IBS-SSS was chosen as it was thought possible that returning 26 week HADS may be related to initial IBS-SSS. It should be noted that the number of events (i.e. number of missing data points) for

HADS was only 17. Therefore following the rule of 1 predictor per 10 events only allows for 1 predictor to be included in the regression equation. This means that the results of the regression should be viewed with caution. However the regression was carried to determine whether it backed up the results obtained from the comparisons made above. The results from the regression are shown in Table 9-16.

Predictor	B	SE β	Wald's x^2	Df	p	e^{β} odds ratio
Constant	-0.033	1.586	0.000	1	0.983	0.968
Age	-0.057	0.028	4.207	1	0.040	0.945
Employment (employed = 1, not employed =0)	2.447	1.120	4.771	1	0.029	11.549
Allocation			3.954	2	0.139	
Allocation (1) usual care =1	-0.867	0.752	1.330	1	0.249	0.420
Allocation (2) IHT = 1	-2.423	1.239	3.824	1	0.051	0.089

Table 9-16: Results from regression model for missing HADS

The regression model indicated that age and employment status are significant predictors of missing HADS scores at the 0.05 level. Employment p=0.029 and age p=0.040. The Cox and Snell pseudo r^2 is 0.244 indicating that the model does not provide a good explanation of the missing data and it is therefore likely that there are other factors associated with missingness. The lack of fit of the model may in part be due to the low level of events and these results should be treated with caution. However as both the p values for the comparisons and the p values in the regression model show that age and employment status are predictors of missing 26 weeks HADS then it is likely that these are indeed predictors. From these results it is believed the data is not MCAR. However the as with the missing 26 week IBS-SSS missingness is not substantial. As with the missing 26 week IBS-SSS a statistican was consulted for advice as to how to deal with the missing 26 week HADS data. It was advised that if the variables associated with missingness are included in an ANCOVA then this will balance the analysis. Hence in the ANCOVA model for the primary outcome age and employment status will be included.

9.1.7 Primary outcome

The primary outcome for this RCT was change in IBS-SSS between baseline and 26 weeks.

Complete case analysis using t-tests

Figure 9-5 shows the range of the change in IBS-SSS for each of the three arms using available data. It can be seen that there is a large variation in the change that people experienced in all of the three arms regardless of how missing data is dealt with. The length of boxes indicate the inter-quartile range and the horizontal lines at the end of the vertical lines extending out of the boxes represent the upper and lower limits of the change in IBS-SSS.

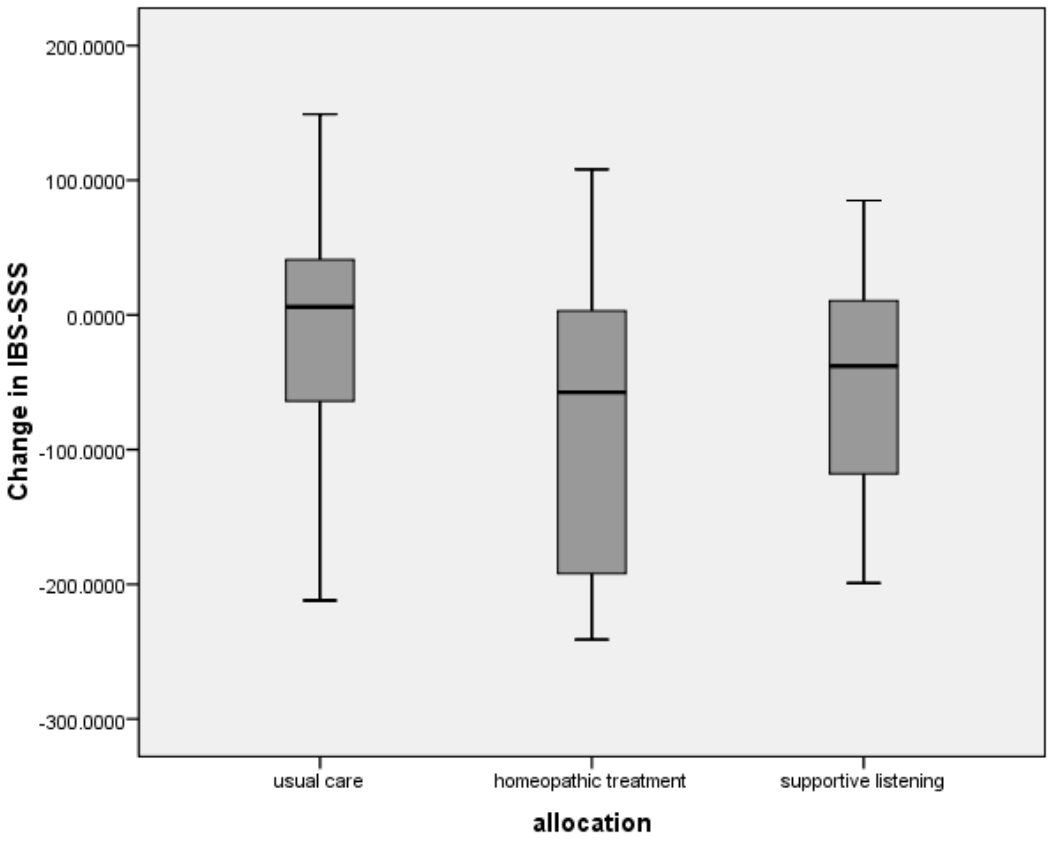

Figure 9-5: change in IBS-SSS by allocation for available data

The change in IBS-SSS for each of the three arms was checked for normality by plotting histograms of the change in IBS-SSS for each arm, plotting normal Q-Q plots, and using Kolmogorov-Smirnov (Massey 1951) and Shapiro-Wilk (Shapiro and Wilk 1965) tests for normality. The results of the Kolmogorov-Smirnov and Shapiro-Wilk tests are given in Table 9-17. A tick in the box means indicates no significant departure from normality and a cross indicates a significant departure from normality. The histograms are shown below (Figure 9-6, Figure 9-7 and Figure 9-8).

Treatment	Kolmogorov-Smirnov	Shapiro-Wilk
Usual care	✓	✓
IHT	✓	✓
Supportive listening	✓	✓

Table 9-17: Results from tests for normality for change in IBS-SSS

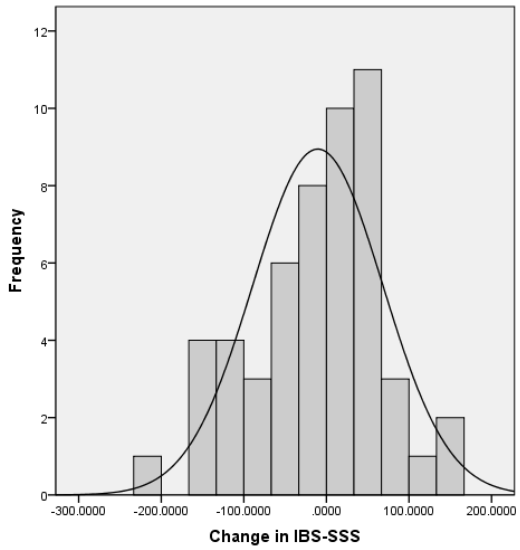

Figure 9-6: Distribution of change in IBS-SSSd for usual care

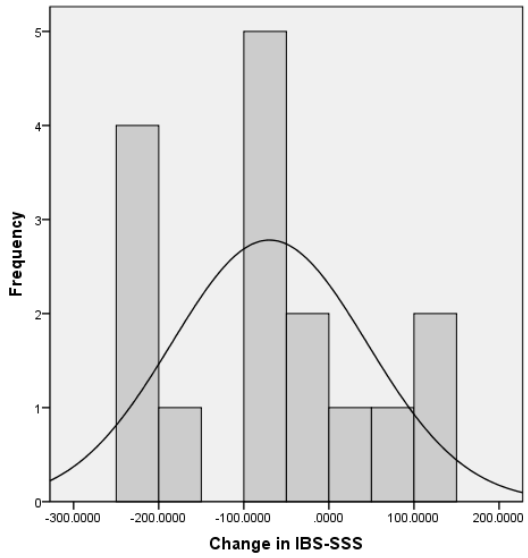

Figure 9-7: Distribution of change in IBS-SSS for IHT

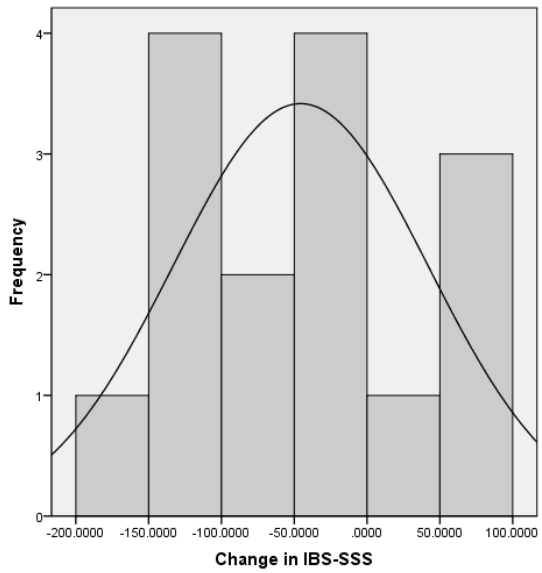

Figure 9-8: Distribution of change in IBS-SSS in supportive listening arm

As can be seen from the histograms the distribution of change in IBS-SSS does deviate from normality. However due to the change in IBS-SSS containing negative numbers it was not possible to apply a natural logarithmic transformation to the data to see if this improved the approximation to normality.

For the available data analysis, despite the deviation from normality seen in the histograms, because the Kolmogorov-Smirnov and Shapiro-Wilk tests did not show a significant departure from normality, it was assumed that the change scores were close enough to normality to carry out parametric tests. Therefore Student's t-tests were used to compare the following, for change in IBS-SSS

- IHT plus usual care versus usual care alone,
- Supportive listening plus usual care versus IHT plus usual care.

Student's t-tests make the assumption that the variability of each group is approximately equal. Levene's test for equality of variance examines whether this assumption has been met. In all of the tests this assumption was met. The result for Levene's test for each of the comparisons is given below in Table 9-18 (when p value < 0.05, the test is not met).

Comparison	Levene's test		Levene's test met
	F	Significance	
IHT versus usual care	3.77	0.057	Yes
IHT versus supportive listening	0.95	0.34	Yes

Table 9-18: Results from Levene's test

Carrying out a Student's t-test to compare the change in IBS-SSS for usual care alone and IHT plus usual care gave change in IBS-SSS of -10.45 and -69.94 respectively with a mean difference -59.48 (95% confidence interval (CI) –109.65 to -9.32); t(67) = -2.37, (p=0.021), i.e. the change in IBS-SSS was 59.48 points greater in the IHT arm compared to the usual care arm. The confidence intervals of the difference do not cross zero (and the p value is < 0.05) hence we can conclude that this difference was statistically significant. The results are shown in Table 9-19. It can therefore be estimated that there is a difference in outcomes between usual care and IHT when the outcome is change in IBS-SSS. The plausible range of the difference between IHT and usual care is likely to be between 9 and 109 points.

The results of a Student's t-test comparing IHT to supportive listening gave change in IBS-SSS of -69.94 and -45.67 respectively with a mean difference -24.27 (95% confidence interval (CI) –51.09 to 99.63); t (29) = -0.66, (p=0.52).Therefore it can not be concluded that there is a difference in outcomes between IHT supportive listening when the outcome is change in IBS-SSS. The results are shown in Table 9-19.

T-test for equality of means							
Comparison	t	df	Sig. (2-tailed)	Mean difference	Std. Error difference	95% confidence interval of the difference	
						Lower	Upper
UC vs HT	-2.37	67	0.021	-59.48	21.13	-109.65	-9.32
HT vs SL	0.66	29	0.52	24.27	36.85	-51.09	99.63

Table 9-19: Results from t-tests comparing change in IBS-SSS

Adjusted analysis

A one way ANOVA was conducted using the complete data. The independent variable was allocation which had three levels: usual care, IHT and supportive listening. The dependent variable was change in IBS-SSS. The covariates chosen were age, employment status and initial IBS-SSS. Age and employment status were chosen because in the exploration of the missing data, age and employment status were found to be potential

indicators of missingness of 26 week IBS-SSS. Initial IBS-SSS was included as a covariate because it is thought likely that there will be a relationship between change in IBS-SSS and initial IBS-SSS.

The homogeneity-of-regression assumption was tested. This test evaluates the interaction between the covariate and the independent variable(s) in the prediction of the dependent variable. This is important because a significant interaction between the covariate and a factor would suggest that the differences of the dependent variable between groups may vary as a function of the covariate. Therefore if the interaction is found to be significant then the results of the ANCOVA would not be meaningful and an ANCOVA should not be carried out (Katz 2006).

The results from the tests between allocation and age, allocation and employment, and allocation and initial IBS-SSS were not significant.

Allocation and age: $F(3,69) = 0.29$, $p=0.83$.

Allocation and employment: $F(3,69) = 0.66$, $p=0.58$

Allocation and IBS-SSS: $F(3,69) = 1.05$, $p=0.38$

Following this the underlying assumption of homogeneity of variance was tested using Levene's test of equality of error of variances the result showed that this assumption had been met.

$F(2,81) = 1.809$, $p=0.17$ i.e. $P>0.05$.

The results from this ANCOVA showed that there were no significant differences between the groups due to allocation. $F(2,73) = 1.83$ $p= 0.167$ $\eta^{2} = 0.048$. A summary of the ANCOVA results are given in Table 9-20.

Source	Sum of squares	Df	Mean square	F ratio	Sig	Partial Eta squared
Corrected model	51838.985[a]	5	10367.797	1.312	.268	.082
Intercept	2095.420	1	2095.420	.265	.608	.004
Covariate – IBS-SSS	2506.684	1	2506.684	.317	.575	.004
Covariate - employment	10496.376	1	10496.376	1.328	.253	.018
Covariate -age	2690.263	1	2690.263	.340	.561	.005
Allocation	28979.227	2	14489.613	1.834	.167	.048
Residual error	576818.913	73	7901.629			
Total	700842.000	79				
Corrected Total	628657.899	78				

Table 9-20: Summary of ANCOVA results for change in IBS-SSS

The parameter estimates for the ANCOVA model are given in Table 9-21.

Parameter	B	Std. Error	T	Sig.	95% Confidence Interval		Partial Eta Squared
					Lower Bound	Upper Bound	
Intercept	-31.977	68.788	-.465	.643	-169.070	105.117	.003
IBSSSS	-.077	.136	-.563	.575	-.349	.195	.004
Employment	26.765	23.222	1.153	.253	-19.517	73.047	.018
Age	-.521	.893	-.583	.561	-2.300	1.258	.005
[allocation=UC]	23.078	29.262	.789	.433	-35.242	81.397	.008
[allocation=HT]	-26.437	33.724	-.784	.436	-93.648	40.774	.008
[allocation=SL]	0[a]						

Table 9-21: Parameter estimates for ANCOVA

a. This parameter is set to zero because it is redundant.
(UC = usual care, HT = IHT and SL =supportive listening)

In summary the results of the ANCOVA showed that the main effect of allocation on change in IBS-SSS was not significant when adjusted for age, employment status and baseline IBS-SSS.

Percentage of participants achieving a clinically relevant change in IBS-SSS

A reduction of 50 points on the IBS-SSS is taken to be a clinically relevant improvement in IBS. (Francis, Morris and Whorwell 1997). Table 9-22 shows the percentage of participants in each arm of the trial that achieved a clinically relevant change in their IBS symptoms.

	Usual care	IHT	Supportive listening
Decrease in 50 points in IBS-SSS	25.0%	62.5%	38.9%
Increase in 50 points in IBS-SSS	18.3%	18.8%	16.7%
Missing	16.7%	0%	11.7%

Table 9-22: Percentage of participants who achieved a clinically relevant change in IBS-SSS

It can be seen that a greater percentage of people in the IHT arm achieved a clinically relevant change in IBS-SSS than in either the usual care or supportive listening arms. However the percentage of people in each of the arms who achieved a clinically significant worsening of symptoms appears similar. No formal tests were carried out on these comparisons.

In summary, for the primary outcome, which is change in IBS-SSS between baseline and 26 weeks, it can be estimated that there is no difference in outcomes between IHT and supportive listening. This was true when both an adjusted analysis that takes into account all the available information on patients is included and when Student's t-test is used to compare IHT and supportive listening.

In terms of IHT compared to usual care, Student's t-test found a statistically significant difference between IHT and usual care, however no difference was found between any of the three arms in the adjusted analysis.

9.1.8 Secondary Outcomes

9.1.8.1 Hospital Anxiety and Depression

Complete case analysis

The change in HADS by allocation was plotted (Figure 9-9). It can be seen that there are two outliers in the IHT arm. The source for the data for these outliers was checked to ensure that no errors had been made in data entry. The data entered was found to be correct.

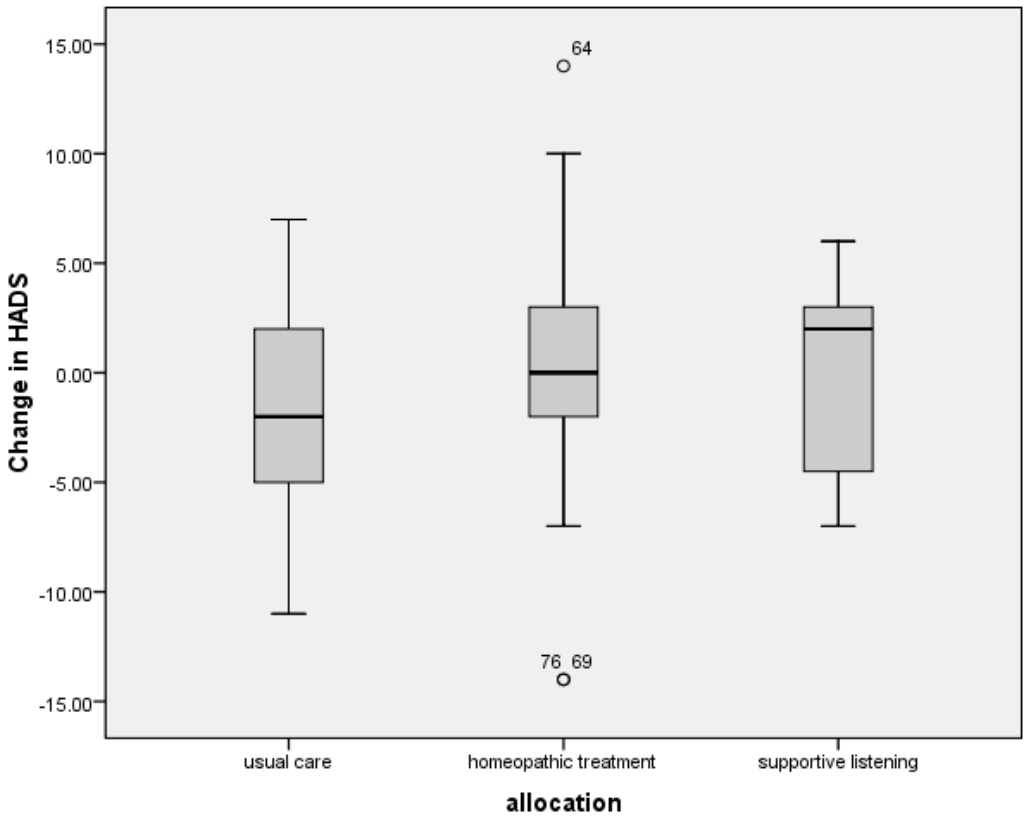

Figure 9-9: Change in HADS by allocation

To ensure that the conditions for t-tests were met the change in HADS for each of the three arms was checked for normality by plotting histograms of the change in HADS for each arm, plotting normal Q-Q plots and using Kolmogorov-Smirnov and Shapiro-Wilk tests for normality. The results of the Kolmogorov-Smirnov and Shapiro-Wilk tests are given in Table 9-23. A tick in the box indicates no significant departure from normality and a cross a significant departure from normality.

Treatment	Kolmogorov-Smirnov	Shapiro-Wilk
IHT	✓	✓
Supportive listening	✓	✓

Table 9-23: Results from tests for normality for change in HADS

Figure 9-10, Figure 9-11 and Figure 9-12 show histograms of the distribution of change in HADS for usual care, IHT and supportive listening respectively.

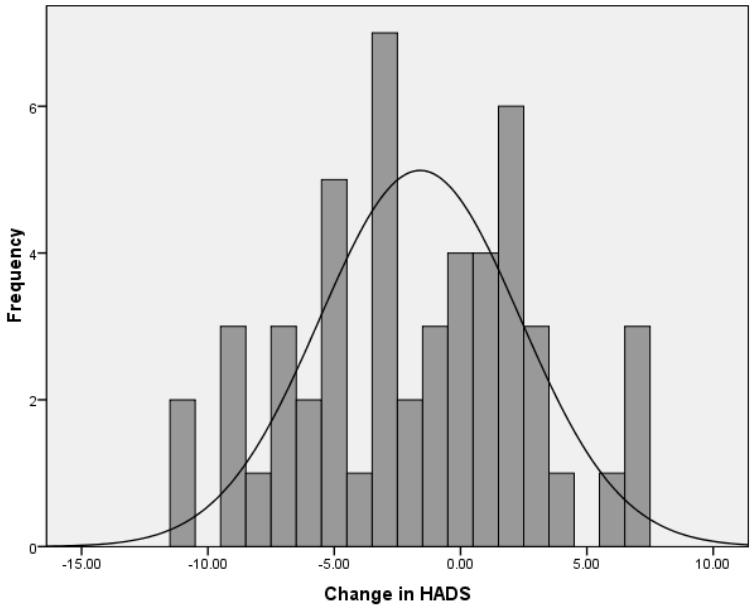

Figure 9-10: Distribution of change in HADS for usual care

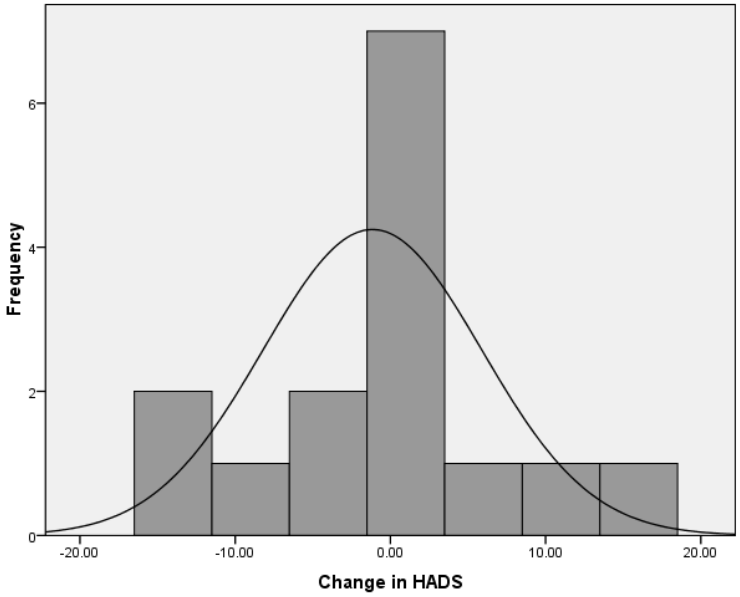

Figure 9-11: Distribution of change in HADS for IHT

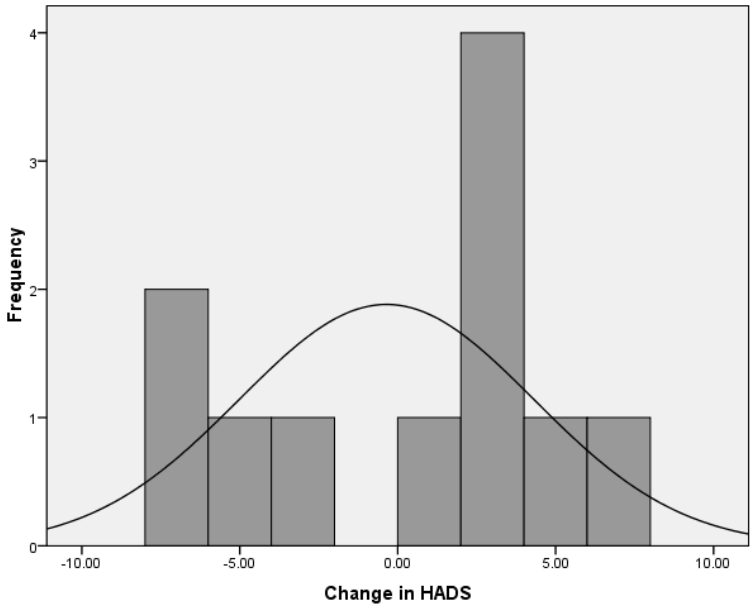

Figure 9-12: Distribution of change in HADS for supportive listening

The results of the Kolmogorov-Smirnov and Shapiro-Wilk showed the data to be normally distributed. The histograms look to be approximately normally distributed, therefore it was taken that the assumption of normality required for parametric tests was met and t-tests were carried out comparing usual care to IHT and IHT to supportive listening.

Levene's test was used to check whether the assumption of equality of variance required for t-tests has been met. In both the comparison of usual care to IHT and IHT to supportive listening this assumption was met, see Table 9-24.

Comparison	Levene's test		Levene's test met
	F	Significance	
IHT vs usual care	2.199	0.143	Yes
IHT vs supportive listening	0.537	0.471	Yes

Table 9-24: Results from Levene's test for change in HADS

Carrying out a Student's t-test to compare the change in HADS for usual care and IHT gave change in HADS scores of -1.78 and -0.20 respectively (where the greater the negative score the greater the improvement) with a mean difference -1.58 (95% confidence interval (CI) –1.59 to 4.76); t(64) = -1.00, (p=0.323), i.e. the change in HADS was 1.58 points greater in the usual care arm compared to the IHT arm. This was not statistically significant at the conventional 5% level. Therefore there was no difference in

the change in HADS scores for those in the usual care arm compared to those in the IHT arm.

The results of a Student's t-test comparing IHT to supportive listening gave change in HADS scores of -0.20 and -1.81 respectively with a mean difference -0.02 (95% confidence interval (CI) –5.34 to 5.38); t(24) = 0.007, (p=0.99). There is no evidence of difference between the improvement in those in the IHT arms compared to those in the supportive listening arm. The results are shown in Table 9-25.

T-test for equality of means							
Comparison	t	df	Sig. (2-tailed)	Mean difference	Std. Error difference	95% confidence interval of the difference	
						Lower	Upper
UC vs HT	0.996	64	0.323	1.584	1.591	-1.593	4.762
HT vs SL	0.007	24	0.994	0.01818	2.598	-5.344	5.380

Table 9-25: Results for t-tests for change in HADS

ANCOVA

A one way ANCOVA was conducted. The independent variable allocation had three levels: usual care, IHT and supportive listening. The dependent variable was change in HADS. The covariates chosen were age, employment status and initial HADS. Age and employment status were chosen because they appeared to be predictors of missingness. Initial HADS was chosen because it was thought that there may be a link between initial HADS and change in HADS. Initial IBS-SSS was not chosen because it is thought that there may be a link between initial HADS and initial IBS-SSS; therefore only one of these measures was chosen as a covariate.

The homogeneity-of-regression assumption was tested. This test evaluates the interaction between the covariate and the independent variable(s) in the prediction of the dependent variable. This is important because a significant interaction between the covariate and a factor would suggest that the differences of the dependent variable between groups may vary as a function of the covariate. Therefore if the interaction is found to be significant then the results of the ANCOVA would not be meaningful and an ANCOVA should not be carried out (Katz 2006).

The results from the tests between allocation and age and allocation and employment were not significant. However the results from the tests between allocation and initial HADS were significant indicating that there is an interaction between initial HADS and change in HADS.

Allocation and age: F (3.62) = 0.34, p=0.80

Allocation and employment status: F (3,62) = 1.87, p=0.14

Allocation and initial HADS: F (2,69) = 7.71 p=0.00

Due to the interaction between initial HADS and change in HADS the ANCOVA model was constructed with only employment status and age as covariates. Interactions between each of the covariates and change in HADS were checked for and this time no significant interactions were found. The results are shown below.

Allocation and age: F (3.65) = 0.43, p=0.73

Allocation and employment status: F (3,65) = 0.06, p=0.98

Following this the underlying assumption of homogeneity of variance was tested using Levene's test of equality of error of variances. The result showed that this assumption had been met.

F (2,69) = 1.48, p=0.23 i.e. P>0.05.

The results from this ANCOVA showed that there were no significant differences between the groups due to allocation. F (2,67) = 0.53, p= 0.591 $\eta^{2 =}$ 0.02. A summary of the ANCOVA results are given in Table 9-26.

Source	Sum of squares	Df	Mean square	F ratio	Sig	Partial Eta squared
Corrected Model	105.917[a]	4	26.479	.936	.449	.053
Intercept	27.257	1	27.257	.963	.330	.014
Covariate - Employment	.135	1	.135	.005	.945	.000
Covariate -Age	38.947	1	38.947	1.377	.245	.020
allocation	29.950	2	14.975	.529	.591	.016
Error	1895.583	67	28.292			
Total	2114.000	72				
Corrected Total	2001.500	71				

Table 9-26: Summary of ANCOVA results for change in HADS

Parameter	B	Std. Error	T	Sig.	95% Confidence Interval		Partial Eta Squared
					Lower Bound	Upper Bound	
Intercept	3.208	3.002	1.069	.289	-2.783	9.200	.017
Employment	-.100	1.445	-.069	.945	-2.984	2.784	.000
Age	-.061	.052	-1.173	.245	-.164	.043	.020
[allocation=UC]	-1.615	1.968	-.820	.415	-5.543	2.314	.010
[allocation=HT]	-.361	2.271	-.159	.874	-4.894	4.173	.000
[allocation=SL]	0[a]						

Table 9-27: Parameter estimates for ANCOVA for change in HADS

a. This parameter is set to zero because it is redundant.
(UC = usual care, HT = IHT and SL =supportive listening)

The parameter estimates for the ANCOVA are shown in Table 9-27.

It can be seen from the results from the t-tests and the results from the ANCOVA that there does not appear to be a difference in outcomes in terms of change in HADS.

9.1.8.2 Empathy of practitioner

The intention was to see if there was any correlation between the perceived empathy of the practitioner (as measured by the CARE measure) and the outcome for the patient in terms of improvement in IBS symptoms. However due to a combination of lower than anticipated participants recruited to the trial, lower than anticipated uptake of treatment (particularly in the supportive listening arm) and failure to return the CARE measure, there was not enough data to carry out any modelling. This is because, following the 10 cases per predictor rule of thumb (Peduzzi *et al.* 1996), only one regression coefficient (including the intercept) could be included in the model. This means that there is not enough data for any predictors to be included in the model and hence no modelling could be carried out. Table 9-28 gives details on the numbers of people who returned their CARE measure.

	IHT (N=16)	Supportive listening (N=18)
Took up offer of treatment	12	9
Returned CARE measure	9	4

Table 9-28: Return rate for CARE measure

Exposure to treatment
The mean number of appointments attended by those who took up the offer of IHT was 5 (SD=0) and the mean number of appointments attended by those who took up the offer of supportive listening was 4.33 (SD=0.87). Further details on how many appointments each participant attended are given in section 9.1.3 Adherence to treatment.

9.1.8.3 Credibility of treatment

The intention was that the practitioners would give the participants the credibility of treatment measure after their second appointment for the participant to complete and return. However the practitioners providing the supportive listening did not like the wording of this measure and did not follow instructions about giving the credibility questionnaires to the participants. The result was that not all the participants in the supportive listening arm of the trial completed a questionnaire and those questionnaires that were completed did not contain the participants' study ID. Therefore it was impossible to link the completed credibility questionnaires to participants as was the intention. The results from the therapeutic rationale question were given earlier in Table 9-5.

As can be seen there were no differences in how effective the participants in the IHT arm (median score 6.00 (IQR: 5.00-7.00)) and those in the supportive listening arm (median score 5.00 (IQR: 3.50-6.50)) thought the treatment would be. However there was a slight difference between how logical participants in the IHT arm thought the treatment was (median score 6.0 (IQR: 5.00-7.75)) compared to those in the supportive listening arm (median score 3.00 (IQR: 3.00-5.50)). This was not tested for statistical significance for the reasons described in Chapter 7.

9.1.8.4 Other comparisons

The baseline data of those who took up the offer and those who did not take up the offer of treatment was compared. Sixteen people were offered IHT and 12 people took up the offer, 18 people were offered supportive listening and 9 people took up the offer. Table 9-29 shows the comparisons between those who took up the offer of treatment and those who didn't take up the offer of treatment.

		IHT		Supportive listening	
		Took up offer n=12	Didn't take up offer n=4	Took up offer n=9	Didn't take up offer n=9
Age	Mean (sd)	43.75 (13.23)	43.75 (13.77)	40.88 (16.56)	44.13 (19.25)
	Missing	0	0	1	1
Employment	% employed	58.3	100	66.7	56.6
	Missing	0	0	1	1
Medication	% taking medication	83.3	75	100	77.8
	Missing	0	0	0	0
Sex	% female	100	100	66.7	88.9
	Missing	0	0	0	0
IBS-SSS	Mean	275.92 (86.67)	293.75 (60.74)	296.11 (84.28)	287.11 (67.88)
	Median	272.50 (190.50-344.25)	275.00 (251.00-355.25)	284.00 (221.50-336.50)	295.00 (228.00-347.50)
	Missing	0	0	0	0
HADS	Mean	15.92 (8.07)	20.25 (7.14)	20.00 (8.28)	14.11 (8.62)
	Median	14.00 (10.50-19.00)	20.25 (12.75-25.50)	18.00 (13.00-28.00)	15.00 (6.50-20.50)
	Missing	0	0	0	0
EQ-5D	Mean	64.42 (14.63)	45.33 (13.61)	51.63 (29.82)	64.88 (19.78)
	Median	67.00 (51.00-70.75)	50.00 (30.00-56.00)	57.50 (23.75-80.50)	68.50 (51.75-79.75)
	Missing	0	0	1	1

Table 9-29: Comparisons between those who took up the offer of treatment and those who did not

58% of those who took up the offer of IHT were employed, compared to 100% of those who didn't take up the offer of IHT. It therefore seems likely that employment status had an impact on whether or not those offered IHT took up the offer. The same difference was not seen in the supportive listening arm where 66.7% of those who took up the offer were employed compared to 56.6% of those who didn't take up the offer. Aside from employment status, there were no other major differences between those who took up the offer of supportive listening and those who didn't.

To summarise, for the primary comparison of interest in this study, the change in IBS-SSS between baseline and 26 weeks using Student's t-test, no difference was found between IHT and supportive listening.

The next chapter reports the results of the qualitative interviews.

10 Results from Qualitative study

Interviews were carried out to obtain information about what, if anything, participants in the active treatment arms of the RCT believed to have helped with their IBS symptoms and general health. The purpose was to provide a greater understanding of what aspects of IHT lead to any improvements in participant's health and what aspects of supportive listening lead to any improvement in participant's health.

Face-to-face interviews were conducted by the author between October 2011 and January 2012. The interviews were semi-structured, lasted between 50 and 90 minutes and generally took place in the participant's home. The interview schedule is given in Chapter 6. All the therapists who provided either the IHT or the supportive listening in the RCT were also invited to interview. The purpose was to provide an understanding as to whether they believed the treatment they provided had helped and if so what they thought it was about the treatment that had helped.

10.1 Participants

Twelve participants in the IHT arm met the eligibility criteria of having attended at least two IHT appointments. All twelve were invited to be interviewed and five consented to interview. Nine participants in the supportive listening arm met the eligibility criteria and were invited to be interviewed. Three consented to interview, although one was subsequently too ill to be interviewed (with a non-IBS related condition), therefore two interviews were carried out. For clarity the participants who had received an active treatment in the RCT will be referred to as "patients" and the participants who had provided the treatments will be referred to as "therapists" from this point forwards.

10.1.1 Patients

All the patients interviewed lived in the Barnsley area and described themselves as being of white British origin. Patient characteristics are given in Table 10-1. Participants' names have been changed to protect their anonymity.

Name	Age	Gender	Treatment received	Number of treatment sessions attended
Sheila	42	Female	IHT	5
Paula	58	Female	Supportive listening	5
Mike	42	Male	Supportive listening	5
Cynthia	55	Female	IHT	5
Elizabeth	50	Female	IHT	5
Sam	26	Female	IHT	5
Rachel	51	Female	IHT	5

Table 10-1: Patient characteristics

10.1.2 Therapists

All the therapists who provided treatment in the RCT were invited to interview (two homeopaths and two counsellors) and all four consented. One of the listening providers, however, was subsequently unable to attend an interview due to a change in work commitments. Therapists' characteristics are given in Table 10-2.

Name	Therapy provided	Qualification	Number of years in practice
Cath	Homeopathy	Member of the Society of Homeopaths	12
Joanne	Homeopathy	Member of the Society of Homeopaths	10
Angela	Supportive listening	Member of the British Association for Counselling & Psychotherapy (BACP)	7

Table 10-2: Therapist characteristics

10.2 Analysis of the interviews

In the assessment of quality in qualitative research there is no consensus as to the criteria that should be used and how these criteria should be applied (King and Horrocks 2010). However documenting the analysis process in a detailed manner has been acknowledged as a means of ensuring dependability of the analysis (Mays and Pope 1995; Thomas and Magilvy 2011). Therefore in the interests of transparency and dependability the analysis process is explained in depth in the following sections.

Dependability is similar to the term “reliability” used in quantitative research. It occurs when another researcher can follow the decision trial that the original researcher used and would be able to come to a similar not contradictory conclusion. The process is described in the results section rather than the methods section because the analysis was a process that occurred in four stages. In order to provide a comprehensive description of the process it was necessary to explain how the findings from one stage led to the analysis of the next stage. The goal of the analysis was to try to explain why and how the treatments had or had not worked.

The four stages to this analysis process were:

- Generating and coding themes
- Charting themes to make connections between them
- Using themes to map out individual patient journeys
- Looking across the patient journeys and themes to develop a typology of different ways in which the treatment was perceived to have worked

A full description of what these stages consisted of will be presented in Sections 10.2.1 to 10.2.4.

10.2.1 Transcription and coding of interviews

All interviews were recorded and transcribed verbatim. The researcher transcribed the first three interviews. The research ethics committee’s opinion was sought on having subsequent interviews transcribed by an employee of the University of Leeds, which was approved. After the first interview was transcribed a coding framework of themes was constructed through reading the transcript and identifying themes that were relevant to the research aims; which were to explain why and how the treatment had or had not worked. This process was guided by the aims of the research, issues raised by the respondent and the topic guide (described in Chapter 6). The themes identified as important within the interviews were:

- the treatment worked
- the treatment didn’t work
- the treatment was helpful
- effect of the homeopathic remedy
- description of the treatment
- description of the therapist

- expectations of treatment
- use treatment again?
- things they tried
- reasons for taking part
- recommend treatment to others

The themes have been presented in the order in which they were discussed in the interviews. These themes emerged through the initial familiarisation phase of reading through the transcripts and were important because they would give an insight into what if anything the patients believed had worked, how they felt it had worked, in what way, and why. Although the “treatment worked” and the “treatment was helpful” initially appear to be related they have been split because though participants may have found the treatment helpful, it may not necessarily have worked in terms of reducing their IBS symptoms. After transcribing the interviews were then coded into these themes. Table 10-3 gives an explanation of what these themes meant and an example of a quote from the interviews that fitted each theme.
During the process of reading and categorising the interviews into the themes listed above, new themes that did not fit into the above list, but that represented key aspects of the participants’ experiences of treatment were added to the framework. After the addition of a new theme transcripts already coded were re-read to determine if there was anything in that transcript that fitted into the new theme. This carried on in an iterative process until all the interviews had been coded. The additional themes added were:

- other health problems
- effect of treatment wore off
- lay theories of why treatment worked
- quality of the talking
- reasons why it had to be the homeopathic remedy
- relationship with food
- set back due to life events

Table 10-4 gives the additional themes, with an explanation of what the theme meant along with an example quote for each theme.

Theme	Explanation	Example
Treatment worked	Descriptions of the treatment working.	"Yes that one was definite. I think I've been showing signs of er, you know improvement but nothing to the level of that particular evening and taking that one which is and I didn't expect that. I don't know whether C. (homeopath) expected it but it happened. And then when I went back to see her and said, oh that was unbelievable" (Elizabeth – IHT) "I mean erm pause erm the sort of clinical side of it erm I don't probably hasn't had any effect. But on the sort of mental side it has" (Mike – supportive listening)
Treatment didn't work	Descriptions of the treatment not working	"Er it's (IBS) actually got, got worse " (Mike – Supportive listening)
Treatment helpful	Descriptions of how the treatment helped them	"You know, so but yes it helped talking to somebody that knew summat, that you could talk, talk about it, you know cos your tell your friends ... say to them like, oh I've got this problem if I need to go to toilet. I've got to go to toilet, but you can't go into detail, because its not nice. You know like and I just when I go, I go and that's it, but like talking to C (homeopath), it were like talking because she understood the feelings and the pain and anxiety of what you're doing, you know like urgency of going to toilet and what kind of poo. You know you had to be careful who were in the next cubicle because you made such a noise, and smell's horrendous absolutely horrible." (Cynthia – IHT) " I've lost that control erm again and err talking to counsellor basically that's what it is I'm losing control. You now what I mean everything everything's just a mess at the moment but talking to somebody has really helped I suppose." (Mike – supportive listening)

Theme	Explanation	Example
Effect of the remedy	What happened after taking the remedy.	"I think it was a couple of days after I took the first tablet and I started going to the toilet, oh no I got home and she said it wont happen today its not like a miracle cure. I'm not giving you a laxative and the following morning I got up and went to the toilet." (Sheila – IHT)
Description of the treatment	Descriptions that were given of the treatment. Any advice that was given lifestyle, diet etc	"Well I wasn't too sure what to expect when I first went to have me first meeting with C. And I was a bit like oh that was quite er, different in so much as it was very much getting understanding of me, and my life style of people around me, and it was more of a probing to get to know me, the personality, the character." (Elizabeth –IHT) "Well we just talked really it was just a talking there was no set thing about it I mean I thought we were just going to talk about bowels but we didn't really we just just just talked really about like you talk in counselling you just talk don't you." (Paula – supportive listening)
Description of the therapist	How the behaved, what they were like.	"She were really good. And like I say, you did, we did go into depth with things. But er, I didn't mind because I'm one of them what, with me being depressed and that been to counsellor and things like that so I've learnt to open up. Erm but er no she were brilliant, she were really good, from first moment I were at ease with her. She were brilliant , yes can't say owt wrong." (Rachel – IHT) "Somebody you felt confident to talk to, made you feel comfortable as I said she er showed she cared to me it didn't felt it were just a job to her." (Mike – supportive listening)

Theme	Explanation	Example
Expectations of treatment	Any expectations they had of the treatment before receiving it.	"No well I knew of it. You know and I had a little bit I suppose one of those what's that all about. is it just a case of it's in the head, and is it a placebo and really is it one of those. So I was probably at best a cynic." (Elizabeth – IHT) "I suppose with A (counsellor) I went there open minded erm not expecting too much" (Mike – supportive listening)
Use treatment again?	Whether or not they would use the treatment again.	"I would go back, I would continue because I did feel the benefit" (Sam – IHT) Well I suppose If my bowels started really bad again and it were offered to me yeah I'd have a go at it (Paula – supportive listening)
Things they tried	Other things they had tried for their IBS, either during the trial or in the past.	"I'd got that point so I went and I saw a urr nutritionist and they suggested I do a complete detox so I had 3 months of apple juice what was it apple juice and cayenne pepper and garlic and all sorts of stuff to do a complete detox and then build the system back up again." (Sheila – IHT) "I mean over the years I've tried sort of taking certain food things out like milk and fibre, things like that but it just hasn't done anything for me" (Mike – supportive listening)
Reasons for taking part	Why they agreed to take part in the trial.	"It wan't costing me anything I have I have lost a husband with skin cancer an I have think an all these years after that they're going to be a pill now that they can swallow and I think any anybody that can help anything in anyway to make the future better for other people should do it if they can." (Paula – supportive listening) "Um I I was fed up with having it and I don't want surgery" (Shiela – IHT)

Theme	Explanation	Example
Recommend the treatment to others	Whether or not they would recommend the treatment to others.	"Oh I would tell them to go and have a talk and get to know a bit about it yes definitely yes. Cos like you say it's er, they can't they can't pin point it down of food allergies or stress. So there's got to be summat that's got to come forward on somebody, somebody must be able to pick summat up. " (Cynthia – IHT) "I'd say yeah recommend it .In fact one of friends who goes to school she actually got er all the information about it. Er and when she applied for it she got the listening and she turned it down, and she said is it good? I said, yeah to be honest yeah, I said if you get offered it again honestly go for it" (Mike – supportive listening)

Table 10-3: Explanation of initial themes

Theme	Explanation	Example
Other health problems	Description of other health problems and the effects of treatment on them.	“Oh gosh yes I mean if any thing I felt, I mean I'm erm I'm fifty one I'm going through the change as well. So I remember saying to C. once flippin hot sweats you know and all of that. And er, don’t know why but the Nux Vom even helped with that, I don’t know whether it picks up you know the body whatever, cos I said to her you know I went though a period where it was like, oh gosh and always in the evening and always when you go to bed and er, I just mentioned it to her because you talk about you know lots of different things.” (Elizabeth – homeopathc treatment)
Effect of the treatment wore off	They were better whilst they were having the treatment but the effects of the treatment wore off.	“Before I'm met C. It were bad and then, it like the six months were fine and then we are back to square one again. You know it's just the time what I were going to C. and talking and gettin' them little tablets it did a world of good. But after that then we were back to square one.” (Cynthia – IHT)
Lay theories why treatment worked	How they thought the treatment worked, what it was about the treatment that led to any effects.	“It seemed to be that she looked at me as a whole, rather than just what I was actually specifically there for, she did look at other things and helped me with that and I suppose things have a knock on effects don’t they, I do believe that if there is one thing wrong in the body then other things get out of balance a little bit. So I think it did seem to regulate and like give that harmony I suppose” (Sam – IHT) “It were just pure talk about whatever and whether this works to I mean yeah, I suppose if you think about it if you got all these things on your mind and that contributes to your bowels getting irritable and starting off. If year go to somebody and just talk and just let it all out then I suppose it probably does ease it. I don’t know.” (Paula – supportive listening)

Theme	Explanation	Example
Quality of the talking	Description of the talking aspect of the treatment, what it consisted of and how it was conducted.	"Being able to talk she believed straight away if you know what I mean. She weren't there just cos she were being paid I felt like she were being there cos she cared. You know what I mean, she listened and then when she were talking she were giving a little bit of feedback like saying, Er saying things like look at the good points you knew she's were listening." (Mike – supportive listening)
Reasons why it had to be the remedy	Reasons why it had to be the remedy that had led to any effects.	Erm, because the first time she gave me something and I said well it did and it did wonderfully. The next time she gave me something different. And then and after a week I rang her up and said I don't know what you've given me but it makes me feel ill and its not done anything. So she sent so she sent me the original one again. (Sheila – IHT)
Relationship with food	The effect of food on their IBS symptom.	"I know it's not what I eat because I've not pinpointed it to anything, because I've tried that myself before I started going to C. Whether it were milk whether it were bread or whether it were owt in particular you know, and it's not it's just one of them things it just does it. So you know I just can't pin point it, it's not tomatoes pips or it's not apples or owt. I've tried and tried and it just does it on it's own like you know I just no control over it really." (Cynthia – IHT)
Set back due to life events	Descriptions of situations where life events led to a set back in their IBS.	"You know what I mean, boosted me up I must admit I had 5 sessions with her up sort of the last session doing really well. erm but then sort of the last session because I've got the tribunal Thursday. It's really sort of knocked me back." (Mike – supportive listening)

Table 10-4: Additional themes

10.2.2 Charting themes

Once all the data had been categorised into these themes, charts were constructed. In these charts the themes were broken down into subthemes, for example “treatment worked” was broken down into nine subthemes, as to how people knew the treatment had worked e.g. two of the subthemes for “treatment worked” were: coping better with life and “reduction in medication”. A full list of the sub themes for “treatment worked is shown in Table 10-5.

Sub theme	Explanation
Non specific “worked”	Non specific statements relating to the treatment working
Other health problems better	Improvements in other health problems they may have been suffering with
Quantifying the improvement	Putting facts and figures to the improvement
Improvement in frequency of toilet	An increase or decrease in the number of visits to the toilet, depending on whether they had constipation or diarrhea prevalent IBS
Coping with better with life	Ways in which they were coping better with their life
Easy	The ease at which the treatment worked
Reduction in medication	Reduction in the amount of medication they were taking
Certainty	How certain they were that the treatment had worked
Improvements mentally and emotionally	Improvements in their mental and emotional state

Table 10-5: Subthemes of "treatment worked"

Charts are tables that contain quotes (or summarised quotes) for each participant for each of the themes or subthemes. Participants may have more than one quote for each subtheme and therefore all quotes relevant to that subtheme are summarised separately rather than synthesising the quotes to produce one synthesised quote for each participant for each sub theme. Table 10-6 shows the basic structure of a chart. For clarity it is vital that participants are kept in the same order for each chart when more than one chart is being constructed (Srivastava and Thomson 2009).

	Sub theme I	Sub theme II	Subtheme III	Subtheme IV	Sub theme VI
Participant I					
Participant II					

Table 10-6: Basic structure of a chart

In this study the unit of analysis was the person rather than the mechanism or theory. Therefore a separate chart was prepared for each theme of interest. Two themes were chosen for full charting, these were, “lay theories about how the treatment worked” and “the treatment worked.” These were chosen because following coding and familiarisation of the data they were found to cover important points that would aid the understanding of what it was about the treatment people found helpful. “Treatment didn’t work” was not used because there was only one quote from Mike in this theme, which is given in Table 10-3. Charts were draw up for these two key subject areas and entries made for all respondents on each chart. To do this all the quotes from all the participants regarding the treatment working were printed off and re-read. After re-reading all the quotes regarding the treatment working, the theme, the treatment working was broken down into subthemes and each sub theme given a title. A chart was constructed with the participants’ names down one side and the titles of the sub themes along the top. The quotes were then placed in the appropriate box. This was repeated for the theme “lay theories as to why the treatment worked.” The sub themes chosen for this theme are shown in Table 10-7.

Sub theme	Explanation
Body working the way it's supposed to	Statements relating to the body working properly and in the way it is supposed to work
Holistic	The treatment looked at them as a whole rather than breaking them down into little pieces
Letting it out	Offloading, letting off pressure etc.
Realisation of self	When they realised things about themselves that either helped them to deal with their IBS or led to them realising what was causing the IBS
Sorting out head	Statements relating to sorting their head out thinking things through, getting things straight in their mind
Action of the remedy	A physical or emotional reaction that they ascribed to being due to the remedy
Combination of remedy and talking	Talking and the remedy both had led to effects
Not the talking	Ways in which they knew it had to be something other than the talking that had led to any effects

Table 10-7: Sub themes for "lay theories as to why the treatment worked"

In the process of charting themes are often joined together or separated as links are made between themes. In constructing the charts in this study it was realised that the theme of the remedy had not been fully explored and further links between the remedy and lay theories about the treatment and the treatment working could be made. Therefore all quotes relating to the remedy were re-read and studied and then incorporated into the charts where appropriate.

Once the charts had been constructed they were printed off and shared with a supervisor with the purpose of identifying gaps, areas that could be further explored and discussing each others understandings of the themes to bring further insights into the data. Following this discussion the charts were

examined to see where there were gaps e.g. which of the subthemes had not been filled in for which of the participants. The interview transcripts were then re-read to determine if there was anything that had been missed and that fitted the gaps. Any such information was transferred to the appropriate place in the chart.
Finally patients reported changes in health (during the interview) were compared with change in their IBS-SSS scores, EQ-5D overall health state (global assessment) and their HAD score. A higher EQ-5D score indicates a higher perceived level of overall health, whilst a higher HADS indicates a worsening of symptoms. This is shown in Table 10-8. These comparisons were made to explore complementary perspectives (Barbour 2001) about how the patients viewed their health and whether or not anything had changed following treatment.

Six of the patients interviewed reported (during the interview) that their IBS had improved, five in the IHT arm and one in the supportive listening arm. IBS-SSS scores confirmed that three of the five in the IHT arm had achieved a clinically relevant improvement in their IBS, one had not changed and one had achieved a score that indicated a clinically relevant worsening of their IBS. A change in IBS-SSS of 50 or more is taken to be clinically relevant (Francis, Morris and Whorwell 1997). One person in the supportive listening arm achieved a clinically relevant improvement in their IBS; this was in agreement with their report during their interview that their IBS was better. The IBS-SSS score for the person in the supportive listening arm who reported that their IBS was the same or possibly worse, was in agreement with this statement, in that the IBS-SSS showed that there had been no significant change in their IBS.

Name	Perceived benefit from treatment reported during interview	Reported Improvement in IBS during interview	Clinically relevant Improvement in IBS-SSS (change of at least 50)	EQ-5D score		HADS	
				Before	After	Before	After
Sheila	IBS improved All other health problems better	Yes	Yes	71	80	12	13
Paula	IBS better	Yes	yes	64	78	15	14
Mike	Mood better Being in a trial helped with self confidence Better able to deal with things	No	No	20	40	33	28
Cynthia	IBS improved Space to talk about mum (who had died) More confident going out (during treatment)	Yes*	Yes	50	67	24	25
Elizabeth	IBS and other health problems improved More aware of body and what causes IBS	Yes	No	75	65	7	17
Sam	Pain better Helped reduce stress in life Realised don't have to be perfect all the time	Yes	No	60	83	10	13
Rachel	IBS improved Mood improved More confident going out	Yes	Yes	30	70	37	23

Table 10-8: Patients' outcomes from RCT

*** Improvement during treatment but wore off when treatment finished**

Sam and Elizabeth reported an improvement in their IBS symptoms at interview; however this was not apparent in their IBS-SSS. In Elizabeth's case her baseline and after treatment scores were approximately the same, whereas Sam's score after treatment was significantly worse than her score at baseline. In Elizabeth's case the homeopath reported that a significant event had occurred shortly after Elizabeth finished treatment which led to her going into a "bad depression". This could account for the lack of change in her IBS-SSS and the worsening in her HAD score (7 at baseline and 17 at 26 weeks). This difference in scores and reported changes allowed for an exploration as to why this should be so. Which, in the case of Elizabeth, led to a greater understanding of her patient journey.

Comparing data in this way and exploring discrepancies can potentially lead to a greater understanding of the data and a fuller explanation of why things have occurred.

Mike who said he felt better mentally, but not physically, did not have a clinically significant improvement in his IBS-SSS, however his HAD score dropped from 33 at baseline to 28 at 26 weeks. His EQ-5D score (a measure of the patients perception of their overall health state) increased from 20 to 40. An increase in EQ-5D indicates an increase in the patient's perception of their overall health. These changes confirm Mike's view on what had improved during treatment.

Rachel felt significantly better mentally following treatment and had been able to reduce her anti-depressant medication. Her HAD score bears this out. It reduced from 37 to 23 indicating an improvement in her anxiety and depression levels.

In summary the patients' views on whether or not they had improved were generally reflected in the results from the RCT and comparing them allowed greater understanding of how the patients had or had not been helped by the treatment they received. Except for Elizabeth, everybody scored higher in the EQ-5D rating of their overall health, indicating that everyone perceived their health state to be better following treatment. Everyone who took part in the interviews said that they felt better following treatment. It is useful to see that, although in some cases their IBS-SSS score had not improved, overall they felt better. This gives a further insight into how the participants viewed their health.

10.2.3 Mapping patient journeys

After the charting had taken place, to further understand the data, the patients' experiences of their IBS and the treatment they received was mapped. This involved constructing diagrams for each patient that mapped the history of their IBS and what elements, if any, about the treatment they felt had helped them. The data used to construct the charts came from the interviews. The charts included any information they gave on what they believed to have caused their IBS and any elements that they felt aggravated it and anything that they had done prior to taking part in the trial that they believed had had an effect on their IBS. These charts built on the themes already identified in the early steps of the analysis. Therefore also included was their perception on whether or not their IBS and/or general health had improved since taking part in the trial, and if so, in what way it had improved. Finally, what it was about the treatment that they perceived to have led to any benefits, was also mapped. Figure 10-1 to Figure 10-7 show the maps for each of the participants.

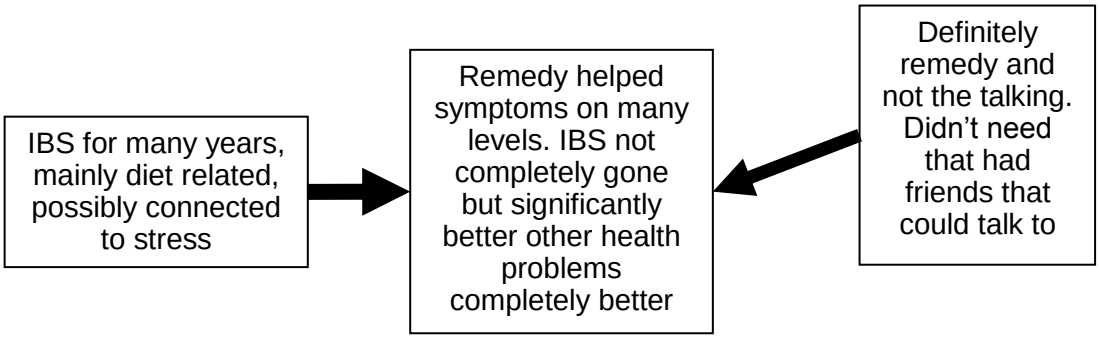

Figure 10-1: Sheila, IHT

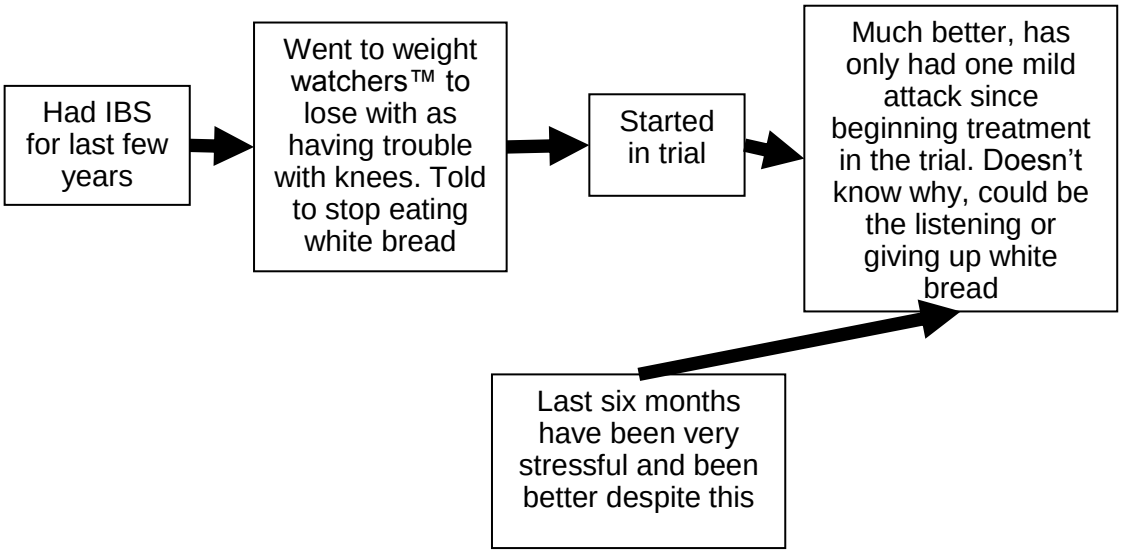

Figure 10-2: Paula, supportive listening

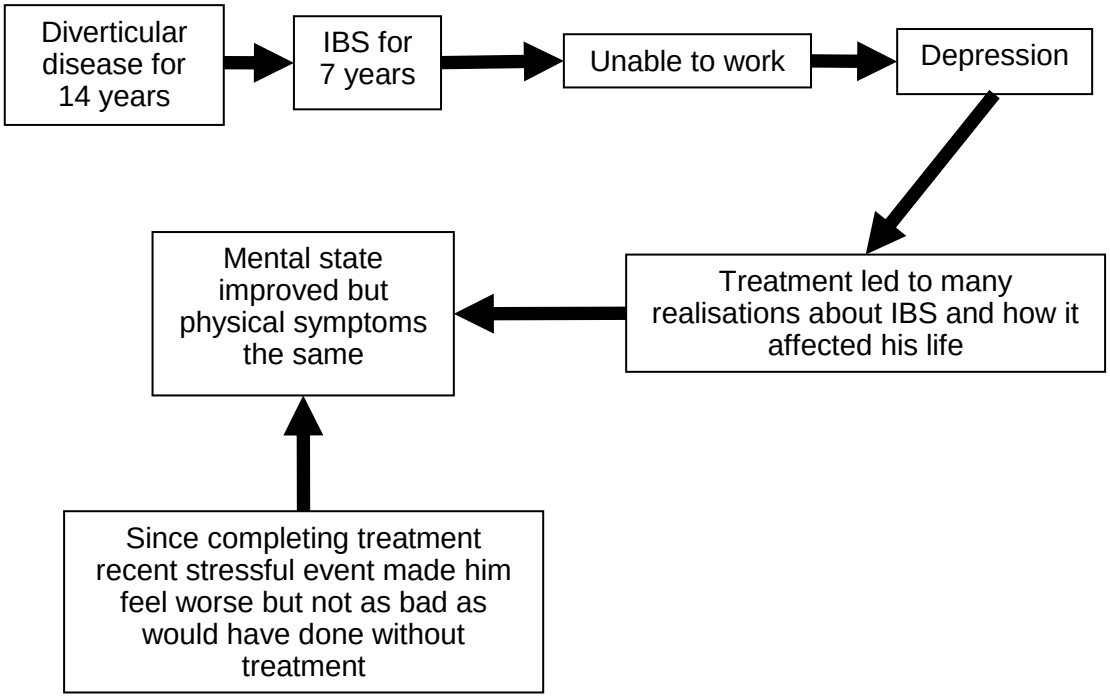

Figure 10-3: Mike, supportive listening

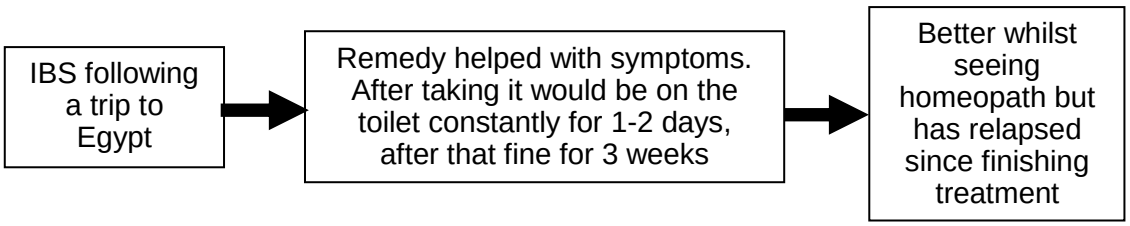

Figure 10-4: Cynthia, IHT

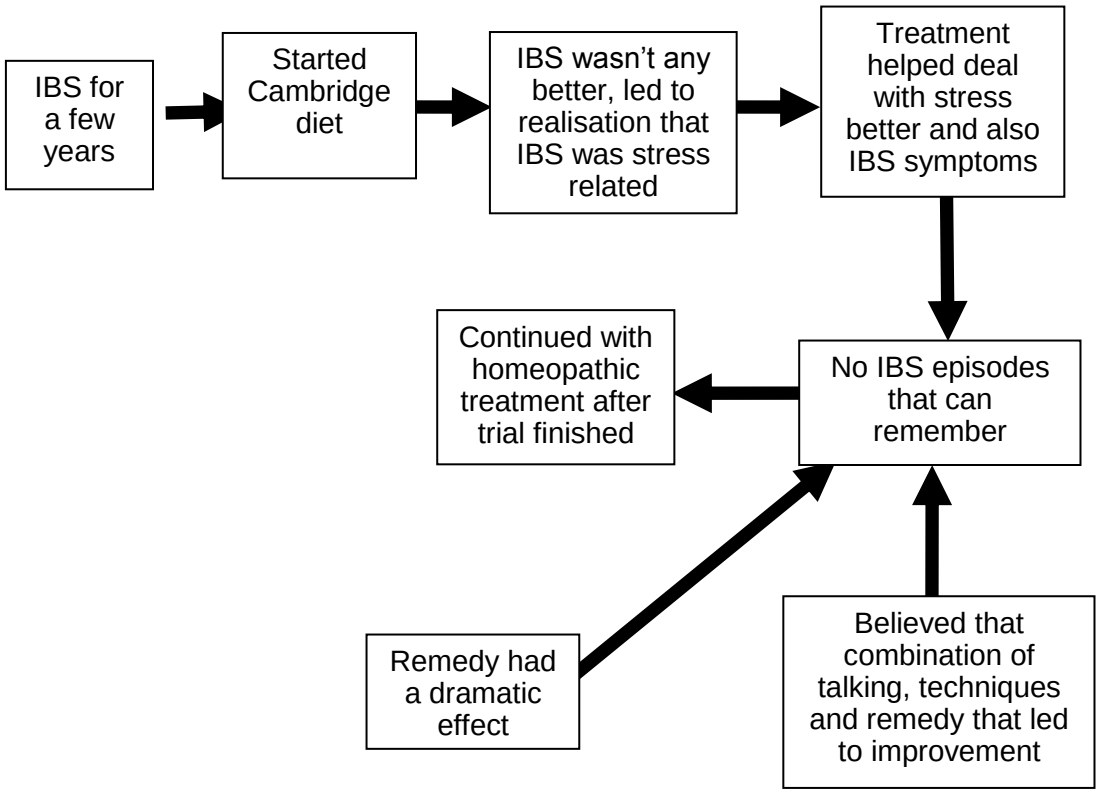

Figure 10-5: Elizabeth, IHT

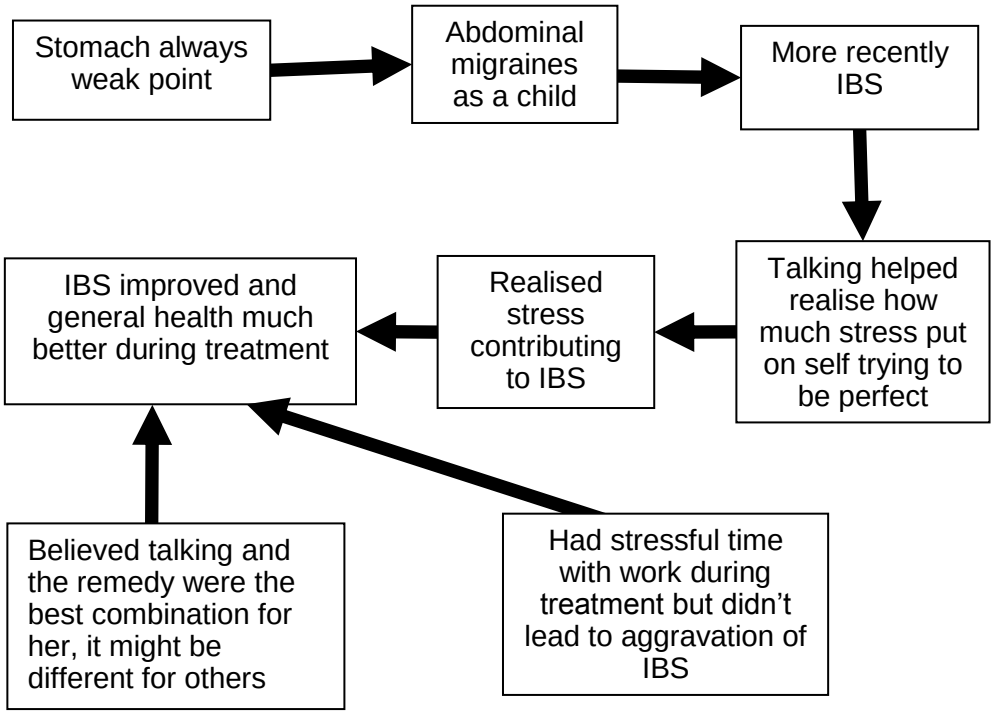

Figure 10-6: Sam, IHT

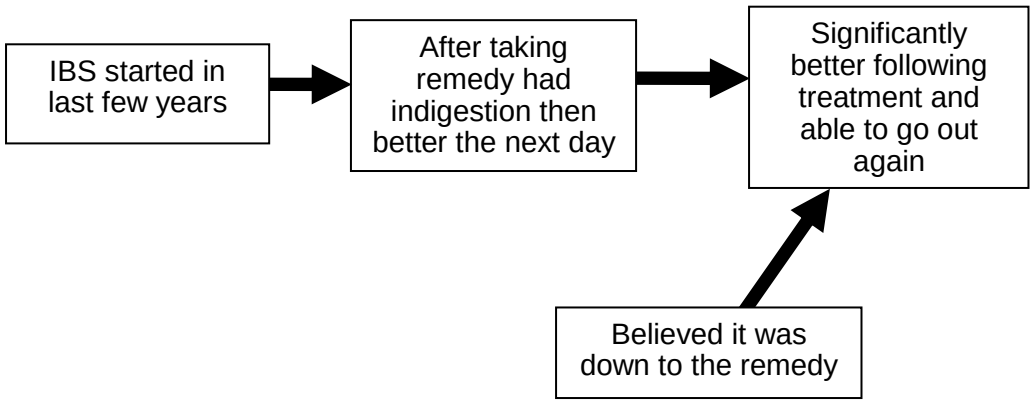

Figure 10-7: Rachel, IHT

10.2.4 Developing typologies

The patient maps and charts were shared with a supervisor. This led to a discussion about the different patients' journeys and the similarities and differences between them. It was apparent that some patients shared similar patterns in terms of whether or not their IBS had improved and what they attributed this to. Sheila and Rachel, who had both experienced a significant improvement, believed their improvement was directly related to the homeopathic remedy, whilst Mike who had received supportive listening, believed the talking had led to an improvement in his mental state. Elizabeth and Sam, who both received IHT, felt that it was a combination of the remedy and talking that had led to improvements in their IBS. Paula who received supportive listening was very uncertain about what had led to an improvement in her IBS symptoms. Discussing these four types led to the idea that they could be thought of as four typologies. A typology is a way of classifying a population or a phenomena such as beliefs into different sectors (Ritchie and Lewis 2003). Each sector can be characterised and is differentiated from the others by its own characteristic elements meaning that each individual can only be assigned to one typology. If the distinction between the typologies allows for individuals to be assigned to multiple typologies then the typologies need further defining. The typologies defined an ideal type, i.e. a more generic description of the four types that allowed for differences between the patients who fitted into a type, yet not allowing the patients to fit into multiple types. The typologies were identified as:

Typology one: Talking helps

Typology two: I'm better but I don't know why

Typology three: It was the remedy

Typology four: It was the remedy and the consultation

For these typologies to hold all patients should be able to be located to a typology. When there is a case that does not fit it should be interrogated to determine whether there is a missing dimension in the typologies or whether another typology needs to be defined (Ritchie and Lewis 2003). In this study Cynthia didn't appear to fit neatly into any of these types. Therefore either another typology needed to be defined or the existing typologies broadened. On re-reading the transcript from the interview with Cynthia and studying her patient journey it was realised that Cynthia believed the remedy had helped her, but after her treatment had finished, her IBS returned to its pre-trial state and the benefits hadn’t lasted. This led to the inclusion of Cynthia into typology three and also the realisation that what was important was what patients believed any improvement was due to. Whilst it is useful to know that the benefits hadn't lasted, in terms of these typologies it wasn't important. Crucial to deciding to which typology a person belonged was what they perceived, if anything, to have benefitted them rather than whether the benefit was sustained.

Once the initial typologies had been identified they needed to be further developed. To do this the themes related to the consultation and talking (letting it out, self realisation and sorting out head) were compared. This was to provide a greater understanding of any differences in people's beliefs about the "talking" in the two treatment arms and between the typologies. Areas of difference and overlap were identified and noted.

Although in this study the participants from the homeopathic treatment arm fell into different typologies from those in the supportive listening arm, the typologies were not simply driven by the nature of the intervention. It is possible that a person in the homeopathic treatment arm could believe that it was the consultation that had helped them and the remedy had no effect. A person with this belief would fit into typology one. Alternatively a person in the homeopathic treatment arm could also have felt better but not have been certain why this was so, therefore fitting into typology two.
Table 10-9 gives a brief description of the typologies and which typology each of the participants fitted into and the treatment they had received.

Typology	Name	Treatment	Description of typology
Typology 1:Talking helps	Mike	Supportive listening	The participant felt better for having talked to someone.
Typology 2: Something's worked but I don't know what	Paula	Supportive listening	Unsure of what had helped, the participant was better but they didn't know whether it was due to the treatment or something else
Typology 3: It was the remedy	Sheila, Cynthia, Rachel	IHT	The participant was better and believed this was solely due to the action of the remedy
Typology 4: It was the remedy and the consultation	Elizabeth, Sam	IHT	The participant felt better and thought that this was due to the action of the remedy and talking to someone

Table 10-9: Description of typologies

Once these themes had been read and compared all the quotes relating to the consultation, the remedy and whether the treatment had worked were organised by the typology the patient had been ascribed to. Views about the consultation, the remedy and whether the treatment had worked were compared across and between typologies. The charts were also revisited and data re-read to further expand the typologies. During this time the interviews with the therapists were listened to and read to identify areas that reinforced what the patients believed and areas where they disagreed. In particular the therapists' views on the talking aspect of the treatment were studied to determine if there were areas of overlap between what the patients and the therapists believed about how talking could lead to a benefit, and what the homeopaths and counsellors believed. The data from the charts, quotes and the therapists was reflected on to produce the typologies, and a chart constructed which contained a summary of each typologies views of what may have helped i.e. the consultation, the remedy or something else, see Table 10-10.

	Consultation	Remedy	Other
Typology one	Shared emotions in a safe environment Believed Insights into connection between mind and body	n/a	n/a
Typology two	Offloading to someone neutral Talking about worries could help reduce worries and IBS symptoms	n/a	Lifestyle change such as change in diet may help
Typology three	Talking about problems was useful but had no therapeutic effect on IBS	Some remedies helped other didn't Sudden improvement after taking remedy Effect of remedy wore off Repeating the same remedy helped Initial aggravation of symptoms after taking remedy	n/a
Typology four	Detailed exploration of symptoms led to a better understanding of what was causing IBS Talking helped to reduce stress	Speed of change (quick) after taking the remedy Effect of the remedy worse off but repeating it helped Aggravation of symptoms after taking the remedy before an improvement	n/a

Table 10-10: Summaries of what each typology believed had helped, from patient's perspective

10.3 Typology one: Talking helps

This typology believed that talking is beneficial and that it had helped them in some way, whether it was solely on a mental/emotional level, solely on a physical level, or a combination of both. They were very certain that they had

benefitted from the talking and were very clear in expressing this. One person, who had received supportive listening fitted in to this typology (Table 10-9).

" Erm but yeah I must admit that work with A has helped a lot. A lot emotionally wise it really has. It helped me enjoy the better days, if anything, now it might not sound a lot to some people but for me, and I suppose anybody else that's like myself its a big thing." Mike (patient, supportive listening)

One of the aspects in which talking helped was that the consultation provided a safe place to share emotions. For Mike this was important because it gave him the opportunity to talk about what was troubling him, the anxieties and doubts without fear of comeback. Talking about these issues relieved the pressure he felt was building up inside him.

"Face to face, just listening it helps brilliantly. You know what I mean, I could let everything out. You know what I mean, all worries how I were feeling and it were just nice it were, like 'pop the lid' cos I feel like friends and family they get fed up of hearing. You know what I mean its like, aint feeling so well like me wife A" why don't you tell me?" "cos I'm sick of repeating myself", feel like I'm repeating myself so like I hide everything." Mike (patient, supportive listening)

Letting out all the doubts and worries not only allowed him to release the pressure that was building up but also aided him in recognising how much IBS had affected his life.

"Being able to talk to somebody let it all out erm makes you realise how much it has affected me. I aint being silly. Sort of it's not my fault I haven't got no control over it, erm and talking to her its made me realise how much its affected me, my lifestyle. How I live, me family, everything else." Mike (patient, supportive listening)

Angela, one of the counsellors who provided the supportive listening, also recognised the importance of being able to share thoughts and feelings that the patient may not have been able to share before. She believed that people had found this opportunity to share and reflect useful and had led to improvements in how the participants felt.

"I think it was a place to actually reflect emotions and feelings that they were unable to share with anybody, whether it was family, because of the fear of burdening family, there was a fear of perhaps medical appointments were not always er, long enough in terms of sharing exactly emotionally how they

felt, and some of what they shared there was some, would have been with other people embarrassment in sharing, but we were in the session because of the confidentiality and because of the er, confidentially of core conditions that were offered they actually went with the process. And were quite happy, and within the supportive listening er, were able to sort of really reflect on themselves, and their positives and the could do's, rather than could not do's. Is often the could not's that block people." Angela (counsellor)

Another aspect of being listened to that helped his typology was that what they were saying was believed. Mike had struggled with people not believing that he was genuinely poorly and so being believed by someone helped to reduce his feelings of self doubt and wondering whether he was really as poorly as he said he was. No one in any of the other typologies mentioned the importance of being believed; however Joanne one of the homeopaths also recognised how important being believed was to the patients.

"One of the things er, that's of value within the homeopathic consultation is that space for somebody to actually listen about your symptoms er and not dismiss them as being (in the mind) most of the patients said that people have said, oh it's in your mind. Your stress, you know. So I think again there is something that I acknowledged about just the space of somebody being able to sit down and someone listen and er, accept and believe that what they are saying is right." Joanne (homeopath)

For Mike talking about how IBS had affected his life also helped with his self doubt in that talking things through allowed him to make realisations about the changes he had had to make to his lifestyle because of his IBS. An example is where he talks about how he now has to take his children to school in the car because he no longer has the energy to walk.

"Think of you know what I mean cos you keep talking and waffling and things come out like simple things like taking my kids to school 200 yards away. Have to use car now so that's one thing that's a total life change." Mike (patient, supportive listening)

The final way in which this typology felt that the talking had helped them was in making the connection between the mind and body. By talking things through they made the realisation that IBS is not just a physical problem but a mental problem as well. Feeling better mentally could therefore lead to feeling better physically which in turn could lead to further improvements in how they felt mentally.

“I must admit that side of it has helped a lot. I think you can, it helps you enjoy the better days. If you can get rid of that. Er emotional side that er psychological side er depression get rid of that. It helps you deal with better days and I don’t know if you had more sort of enjoyed better days more whether then the symptoms start to ease a little bit because some of it some days have got to be triggered through being fed up.” Mike (patient, supportive listening)

All these aspects of talking helping were synthesised into a diagrammatic representation for this typology which is shown in Figure 10-8.

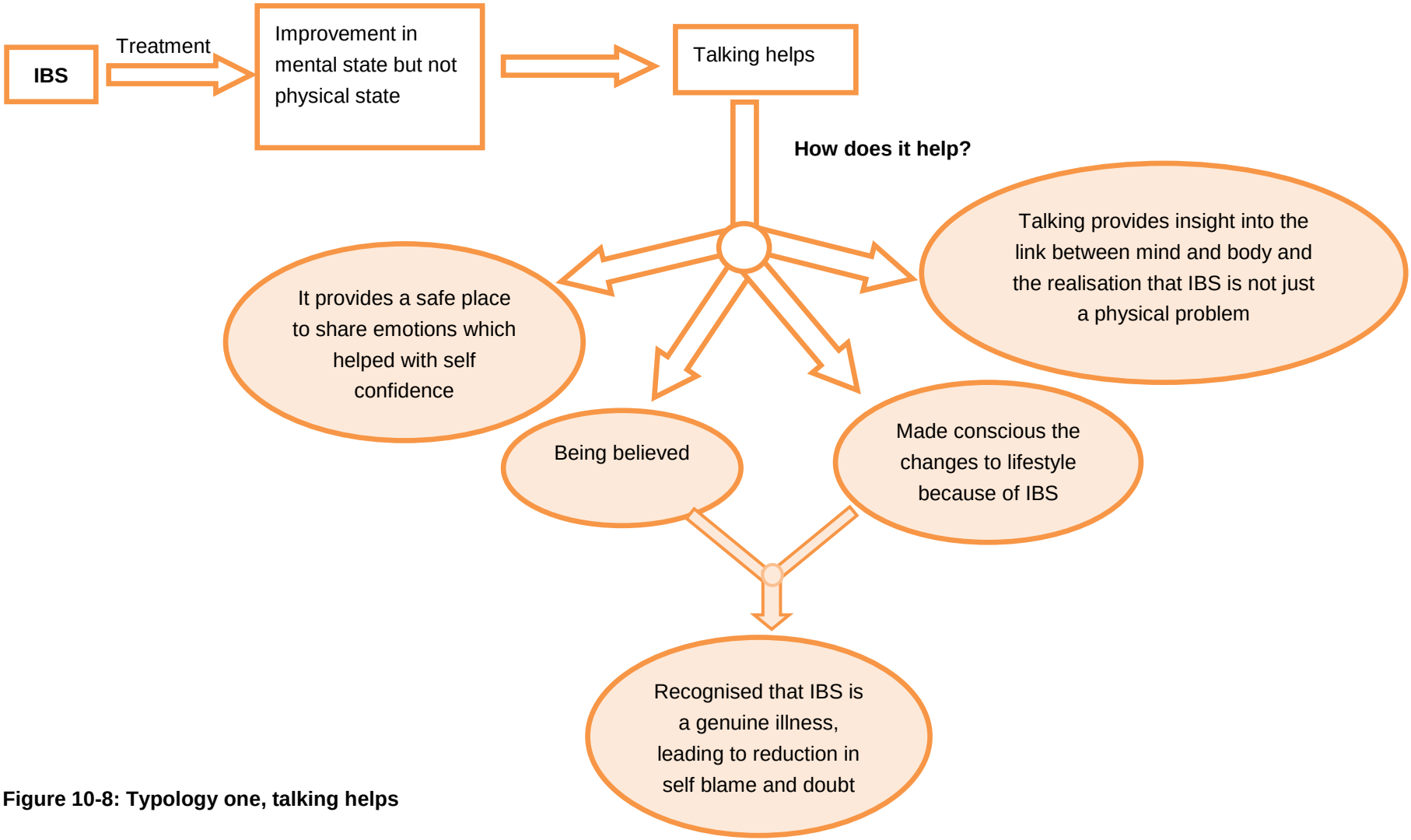

Figure 10-8: Typology one, talking helps

10.4 Typology two: I'm better but I don't know why

This typology did not know what had led to an improvement in their IBS. They did not know if the treatment they had received had helped, it might have done but they weren't really sure. This was in part due to their uncertainty about what had caused them to have IBS. They thought it could have been due to stress or it could be due to some other factor such as diet. This uncertainty led them to an uncertainty about why they were better. If it had been stress that had been causing the IBS then it could have been talking that helped. However, if it was down to some other lifestyle factor such as eating a particular food, then stopping eating that could have helped. One person who had received supportive listening fitted into this typology (Table 10-9).

They thought that having someone to talk to could help with reducing stress, particularly if their IBS was triggered by having something on their mind. If this was the case then talking to somebody could ease it.

"It were just pure talk about whatever, and whether this works to, I mean yeah I suppose, I suppose if you think about it, if you got all these things on your mind and that contributes to your bowels getting irritable and starting off. If you go to somebody and just talk, and just let it all out, then I suppose it probably does ease it, I, I don't know." Paula (patient, supportive listening)

The difference between this typology and typology one was the uncertainity in typology two about whether or not it was the talking that had helped. Improvements could have been due to the talking or they could have been due to some lifestyle factor such as diet. In the case of Paula she was on a diet and cut out white bread at the same time as taking part in the RCT. She wonders whether it was the cutting out white bread that led to the improvement she experienced.

"I don't buy white bread anymore I only buy wholemeal bread an,an it just registers that that's the one thing I did do an I've been aright just had one mild bout. So was it the wholemeal bread. I just do not eat white bread at all. So it makes you wonder dunit?" Paula (patient, supportive listening)

They acknowledged that they had found the talking helpful but didn't really know whether this had any effect on their IBS. Talking probably would be helpful, but whether or not it could help to lead to an improvement in their IBS symptoms, they weren't really sure.

“I probably did find it helpful ,but I think anybody that went to see somebody that, that they had no, erm, that they didn’t know and they could just talk to and they listened without people butting in putting their you know penneth in about what happens would find it helpful to just unload wouldn’t the?” Paula (patient, supportive listening)

Angela, one of the therapists who provided the supportive listening, also felt the supportive listening sessions provided an opportunity to share and reflect on thoughts and feelings. Her experience was that patients were able to share thoughts that they had not shared with anyone before and this was important.

“It was a place for them to share, and reflect also. Er and I suspect, well I know some of the reflections and these were people who er, were not ,not young people they were several decades in terms, had certainly not shared er some of their feelings and thoughts processes, and the challenges to their own dignity that they had felt in relation to their treatment and how it impacted on daily life. In terms of very much limiting them.” Angela (counsellor)

It should be noted that of the people interviewed only Paula reported that she had made another change/done something differently that she felt could have led to her improvement. No one in the other typologies mentioned doing anything else (such as making a dietary change) that they felt had have helped with their IBS during the trial. This may be because they genuinely hadn’t done anything else that had helped with their IBS or it could be that they had made changes but had forgotten that they had made them. Although they were asked about other things they may have done that could have led to an improvement it is still possible that they had forgotten.

This typology is represented diagrammatically in Figure 10-9. Which shows the two main aspects of this typology which are; the possibility that talking could have helped and the possibility that it could have been something else that helped.

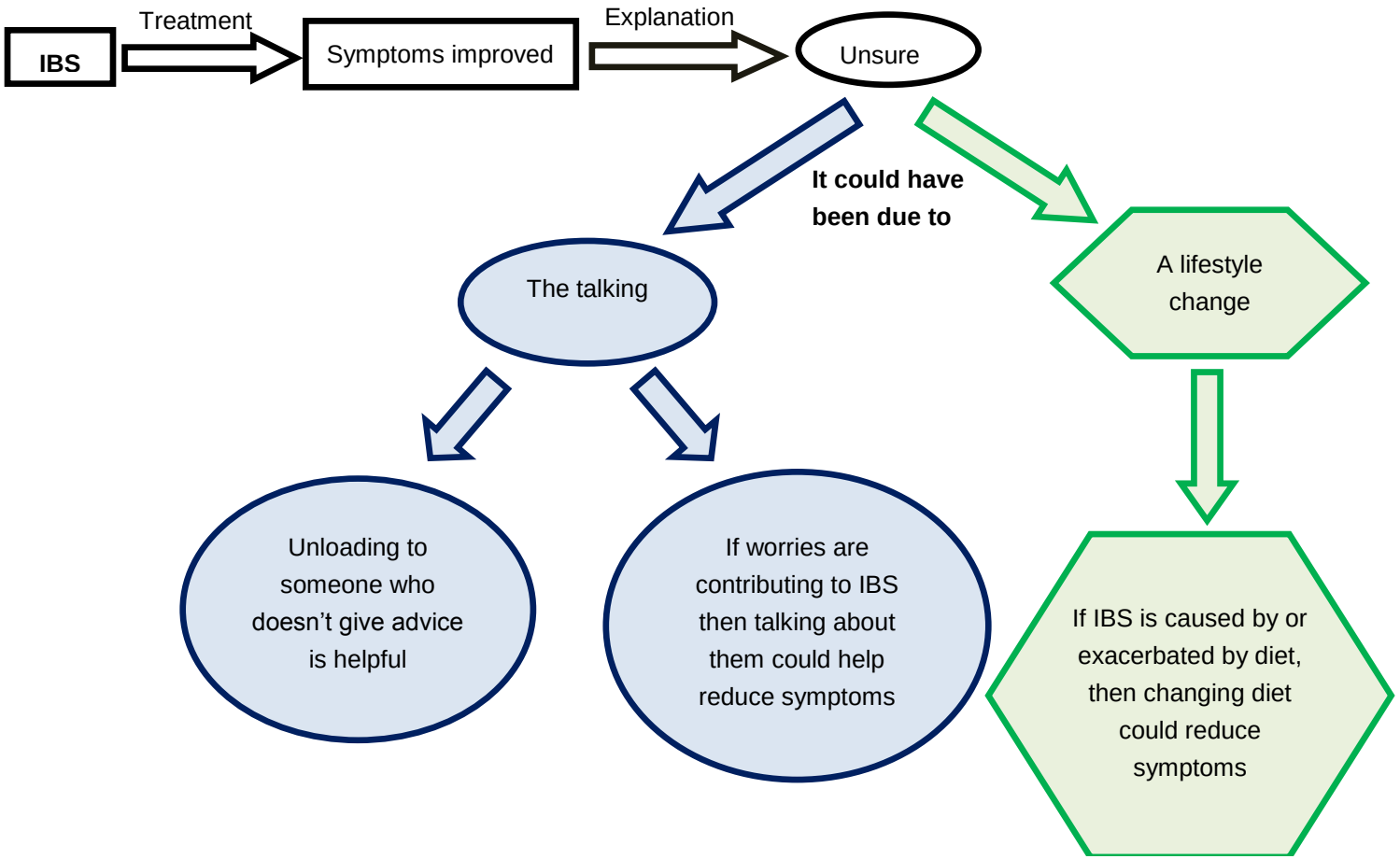

Figure 10-9: Typology two, uncertain what had led to benefit

10.5 Typology three: It was the remedy

People belonging to the third typology believed it was the remedy that had helped them and that the talking was incidental. Three people all of whom received IHT fitted into this typology (Table 10-9). They were very certain that it was the remedy that had helped.

"It had to be the remedy. I know were were chatting but we were more chatting about all and sundry. Rather than and it wasn't chatting about how to treat it and how I might think about treating myself internally it was just chatting, erm and history of what symptoms I've had. For years like I've always always had dry skin" Sheila (patient, IHT)

The interviews with the homeopaths were studied to find similarities or differences between the patients' understanding of why it had to be the remedy and the homeopaths' understanding. Four points were identified that led the patients to the belief that it had to be the remedy that had helped them. These were: the speed at which changes took place, a worsening of symptoms before an improvement in symptoms, not all remedies were beneficial and if the effects of a remedy wore off repeating that remedy led to continued benefit. Although these four points were identified by patients the patients in this typology didn't necessarily experience all four.

The first point that led people to thinking that it had to be the remedy was the speed at which the changes took place. In the case of Sheila she noticed a sudden improvement within a couple of days of having taken the remedy.

"So it's definitely had a sudden improvement, which is why how I know it was the homeopathic remedy." Sheila (patient, IHT)

Cath, one of the homeopaths, felt that improvements due to talking would take more time, taking place over a few consultations rather than immediately.

"I did feel with these it was so easy you know sort of there wasn't time for it to be that really (the talking)" Cath (homeopath)

The suddenness of the changes, therefore, were important in people's understanding of why it had to be the remedy rather than talking. However the speed of action of the remedy didn't always lead to an immediate improvement. The second reason that people believed the remedy to have had an effect was because they experienced a brief worsening of their symptoms prior to improvement. Cynthia and Rachel noticed that they were

worse the day they took the remedy after which they would experience an improvement in their symptoms.

“I mean I would be all day on toilet, up and down, up and down, and then after that then, it were just a normal, it were a just a normal poo, and a normal carry on, you know without thinking, oh I daren't eat that ....you knew you were going to be fine..” Cynthia (patient, IHT)

“they give me bad indigestion and heartburn, I had to sit up all night. But, two or three days like that it's worse, then months, a couple of months I've had (of being better)... it's been brilliant.” Rachel (patient, IHT)

A third reason why participants felt it had to be the remedy was that different remedies had different effects. They may have been given a remedy that helped them and then subsequently been given a different remedy that they felt didn’t do anything or they may have been given a remedy that had no effect and then on being given a different remedy noticed a dramatic improvement. Rachel experienced a big improvement soon after one of the remedies she was given, having found the first remedy not to have any effect.

“*The other ones they didn’t seem to do much, but soon as I had that one... I don’t know but I put it down to that. Them tablets.*” Rachel (patient, IHT)

The use of the word “soon” in this quote from Rachel also demonstrates the speed with which the remedy acted. In contrast Sheila was given something initially that had a big effect but when the homeopath changed the remedy at the next consultation she felt that the new remedy didn’t do anything.

“Erm because the first time she gave me something and I said well it did wonderfully. The next time she gave me something different. And then and after a week I rang her up and said I don’t know what you’ve given me but it makes me fell ill and its not done anything.” Sheila (Patient, IHT)

Experiencing different actions with different remedies was important in people’s understanding of what it was that helped them. The fact that some remedies helped while others didn’t, was confirmatory that the remedy had had an effect. Participants then would ask for a repeat of the remedy that they felt had helped them when its action wore off. In classical homeopathy it is recognised that the action of a remedy may wear off and thus it may need to be repeated (Kent 1984). Cath the homeopath saw the fact that patients asked for repeats of remedies to be confirmatory of the action of the remedy.

“*They did because they asked for repeats. So and I think if you ask for repeat and you get the benefit then, that's fairly confirming.”* Cath (homeopath)

Joanne, the other homeopath, approached treating the patients slightly differently to Cath, who tended to give the participants one remedy at a time. Joanne tended to give them one remedy that fitted their whole symptom picture (a constitutional remedy) along with what she termed an acute remedy to help with any flare ups they may have. The acute remedy was to be taken if and when a flare up occurred, therefore this remedy would only be taken if they had a flare up. Thus the constitutional remedy aimed to reduce or eliminate the number of IBS attacks, along with improving the patients overall health, whilst the acute remedy taken at the beginning of an attack aimed to shorten its length. Joanne experienced participants asking for a repeat of the remedy they felt had helped them and often this was the constitutional rather than the acute remedy.

“It was really interesting that people came back and said just that. You know I have been okay. But I would like some more of that (the constitutional remedy), that remedy because it's been a really stressful month.” Joanne homeopath, talking about the constitutional remedy which was aimed at helping to prevent participants getting the IBS symptoms in the first place.

Cynthia noticed that when the tablets were wearing off her symptoms came back, she would then be better again after repeating the remedy.

“As you were getting to end of your three weeks it were coming back, so you knew then your tablets had worn off.” Cynthia (patient, IHT)

Participants experienced a combination of these factors and it was this that led them to the conclusion that it was the remedy that had led to the effects rather than anything else. These observations fitted with the homeopaths beliefs. It is likely that it is not just one but a combination of these factors which are interrelated that led to the belief that is was the remedy that led to any effect. Figure 10-10 is a diagrammatic representation of these factors.

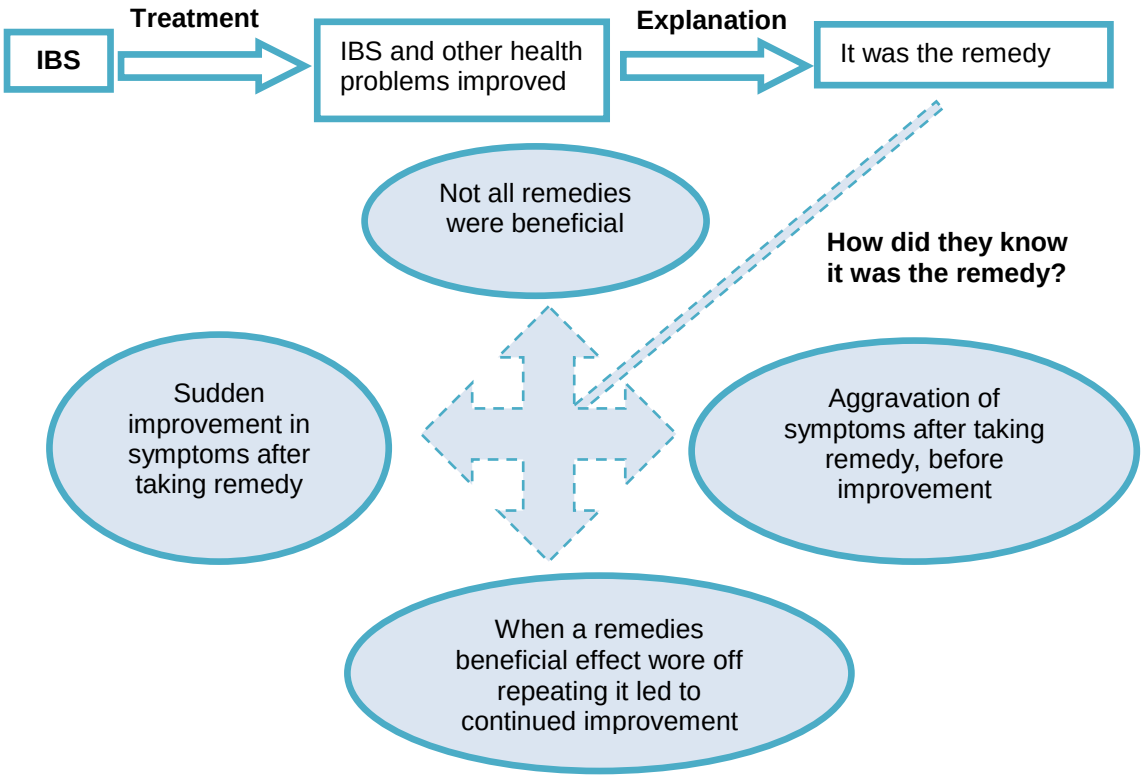

Figure 10-10: Typology three, it was the remedy

10.6 Typology Four: It was the remedy and the consultation

These participants believed it was the combination of the consultation and the action of the remedy that led to an improvement in their symptoms. Two people who had received IHT fitted into this typology (Table 10-9). Their beliefs about how the consultation had helped them centred around how the style of the consultation developed their insight into what led to them getting IBS. Crucial to this was a better understanding of their bodies. This understanding they perceived to have come about through talking about their symptoms with the homeopath and the exploration of their character that is part of the homeopathic consultation. This is subtly different to typology one in that in typology one the perceived benefits were around the themes of off loading, letting off steam and how discussing the impact of IBS on their life had led them to make realisations about how having IBS had affected their mental state. Whereas in typology four because the homeopathic consultation requires an in-depth understanding of bodily complaints and how the patient experiences them the self-exploration it

promoted appeared to be on a deeper level. Mike (typology one) and Sam and Elizabeth's (typology three) experiences were subtly different. For Mike supportive listening facilitated an exploration of the impact of IBS on his life both physically and emotionally.

"So I suppose if I can get head sorted out and enjoy the good days there's always a good chance that I'd have more frequent good days...And they might be more prolonged and I know won't obviously cure it. But it might give me better days and longer days er might even take the edge of flare ups they might not be as severe. Because there's nothing else sort of driving it if you know what I mean." Mike (patient, supportive listening)

However Sam started exploring aspects of her character that could have contributed to her getting ill.

"I have never realised that I'm somebody who just has to have such control over everything, and have to do everything above and beyond, and I think I'm not helping myself at all putting all this stress on myself. And like I said it has helped me look at that and try and take a little bit more of a light hearted view, and I can remember one day I had been sat in the garden just feeling really content just in the house. My boyfriend was watching football or something here I was in the garden, the dog was just pottering about. I just thought this is brilliant. I could just do this for ever. And I can remember getting these feelings of contentment I said to her, I really feel content at the moment, and she said it could be you know with me not putting so much pressure and worry on myself that I'm realising well what you have got to around you is amazing you know stop rushing about and just take stock of what you have." Sam (patient, IHT)

In the case of Sam and Elizabeth IHT was accompanied by a deep reflection of themselves and their symptoms. This in turn led to a greater understanding of themselves. Both Sam and Elizabeth felt a benefit from understanding themselves better.

"*So I think with her trying to, she also pointed out to me that I am vey much that I everything has to be perfect, I don't like to under do anything. I'm not happy with myself and I never cottoned onto this. And I just always wanted everything to be perfect. And I do believe yes perfect is not always existing, but I always want the best of what every I do, and I think she actually helped me in a way realise that you can sometimes just drop below that and it's nothing bad is going to happen, and I think that took some of the stress away."* Sam (patient, IHT)

“cos I think by talking things through you have a better understanding erm, and how your body reacts and feels and, what is it that makes it feel that way, if that makes sense.” Elizabeth (patient, IHT)

Another aspect of this understanding themselves better was the realisation of the need to reduce stress in their lives which could in turn led to a reduction in symptoms. This is similar to typology one where the talking also helped them to make connections between their mental/emotional state and their IBS symptoms. However the difference between these typologies being that in typology one although they had made some realisations they had yet to act on them.

“If you can get rid of that. Er emotional side that er psychological side, er depression get rid of that, it helps you deal wi with better days and I don’t know if you had more sort of enjoyed better days more whether then the symptoms start to ease a little bit because some of it some days have got to be triggered through being fed up.” Mike (patient, supportive listening, typology one)

Elizabeth and Sam both attributed their IBS in part to stress, although they only realised this through taking part in the trial. Having made this connection they felt that reducing their stress reduced their IBS symptoms.

“But I'm getting better I'm understanding it now. Which is helping everything because I think if I can lower my stress then I'm going to lower the risk of these outbreaks. So I think that’s a big thing for me. Learning to relax. And sitting still and I think I did that more during the treatment.” Sam (patient, IHT)

“I think I get a natural build up and then the way it sort of like releases itself is in the stomach form of the IBS. So it was an interesting time.” Elizabeth (patient, IHT)

Sam also felt that offloading and talking helped to reduce her stress levels.

The consultation therefore was a key aspect of treatment for people in this typology. The homeopathic consultation helped them to understand themselves more and make changes, such as reducing stress, these changes helped with their IBS. The act of talking and offloading could also help them to reduce their stress levels. However despite their understanding of how the consultation had helped them they still believed that the remedy had had an additional effect. It was both these aspects combined that led to their improvements. As Elizabeth summarises when reflecting on the dramatic effect of one of the remedies she took

"*I think I think the whole combination. I think you know if I go through it now, and think you know what if I had just gone along and somebody had given me some nux vom would have had the same impact, you know I don't know whether it would. Because I don't think I would have been aware of me and my symptoms and the causes. And all of those things, I don't think maybe it would have had the same impact."* Elizabeth. (patient, IHT)

In terms of how they knew the remedy had had an effect their reasoning was similar to those in typology three who believed it was solely the remedy that had had any effect.

Elizabeth noticed a dramatic improvement in her symptoms after taking one particular remedy.

"So that was a big, I mean talk about er, take something instantly have a reaction then the feeling of like wow. That was yes." Elizabeth. (patient, IHT)

She had never experienced anything like this before, even with conventional medicine. The sudden improvement was preceded by a brief worsening of her symptoms both of which she attributed to the remedy.

"Within two hours of taking this pill, I felt rubbish, pants. I felt my stomach felt bloated. I felt headachy and I felt oh my god I'm having a reaction but the next day when I woke up. I was great." Elizabeth (patient, IHT)

The combination of worsening of symptoms followed by a dramatic improvement confirmed to Elizabeth that it was the remedy that had had the effect.

Sam also noticed a prompt reaction after taking a remedy aimed at supporting her in stopping the contraceptive injection. This quick reaction dropped off after the trial had concluded.

"so when she did that and she did give me something to help with, er, stopping the injection even that I didn't expect anything to happen for months and she got something happening two or three days later... and I never thought anything could be so effective so quickly. But I know it's definitely slowed back down since I'm not seeing her." Sam (patient, IHT)

This is similar to Cynthia's experience of being better whilst having treatment and then getting worse again once the treatment stopped. They both ascribed this worsening to no longer taking the remedies.

Like those in typology three (it was the remedy) both Elizabeth and Sam experienced sudden improvements, or a worsening of symptoms followed by an improvement, which they believed were due to the remedy. In Sam's

case this wasn't sustained after concluding treatment. This was further evidence of it being the remedy that caused the effect. Since concluding the trial Elizabeth has continued to seek IHT and when she feels things are slipping she asks for a repeat of the remedy that had the dramatic effect.

"And also I think I know that if I do need any medicine. I just say to C. I need some of that ... and yes. You know err, and I, I continue down the homeopathic route definitely. I have not gone back to the doctors, not gone back there at all. Erm I've not needed to." Elizabeth (patient, IHT)

This typology is the most complex of the four typologies, not only are there a combination of interrelated reasons as to what it was about the consultation that helped, but also a combination of reasons as to why they believe the remedy played a part. Joanne, one of the homeopaths, saw an improvement in the patients' anxiety symptoms and their physical symptoms. Her view was that the listening could have helped with the patient's anxiety or stress, and although these symptoms can be linked with the physical symptoms, she felt that supportive listening would have been less helpful with the physical symptoms, especially if they were not solely related to stress. This fits in with this typologies view that it is both the consultation and the remedy that has helped.

In summary the patients in this typology saw this whole process as intertwined and saw a need for both the remedy and the talking to help with their IBS symptoms.

"I don't know, I would say definitely both because er with the treatment I felt the effects on different things in the body, but I think the talking helped as well." Sam (patient, IHT)

In homeopathic thinking a correctly chosen remedy should cover the totality of the patient's symptoms, including mental and emotional symptoms, and a well chosen remedy should lead to the reduction in unhelpful behaviour patterns that lead to physical symptoms, such as the need for perfection as described by Sam (Sankaran 1999). In addition homeopaths are taught to discuss with the patient possible maintaining causes, i.e. things that are hindering the patient in getting well, this could include poor situations or relationships (Roberts 2001). In Sam's case this could be her tendency to seek perfection in everything she does. Cath explains this linking of a patient's symptoms and what she perceives to be causative factors and how she feeds this back to her patients.

“So what I will do is I will give a remedy and then if it's a good effect I will explain what I gave and why. And explaining that I had linked this emotional symptom and that physical symptom. So that’s kind of giving them the feedback. That you know either you know you can look at your lifestyle or you will know if you are majorly stressed you are likely to get a return of symptoms and you are likely to need another remedy.” Cath (Homeopath)

Thus to homeopaths the remedy and the talking are deeply interconnected, and those in Typology Four believed both these aspects led to a benefit.

Figure 10-11 gives a diagrammatic representation of typology four.

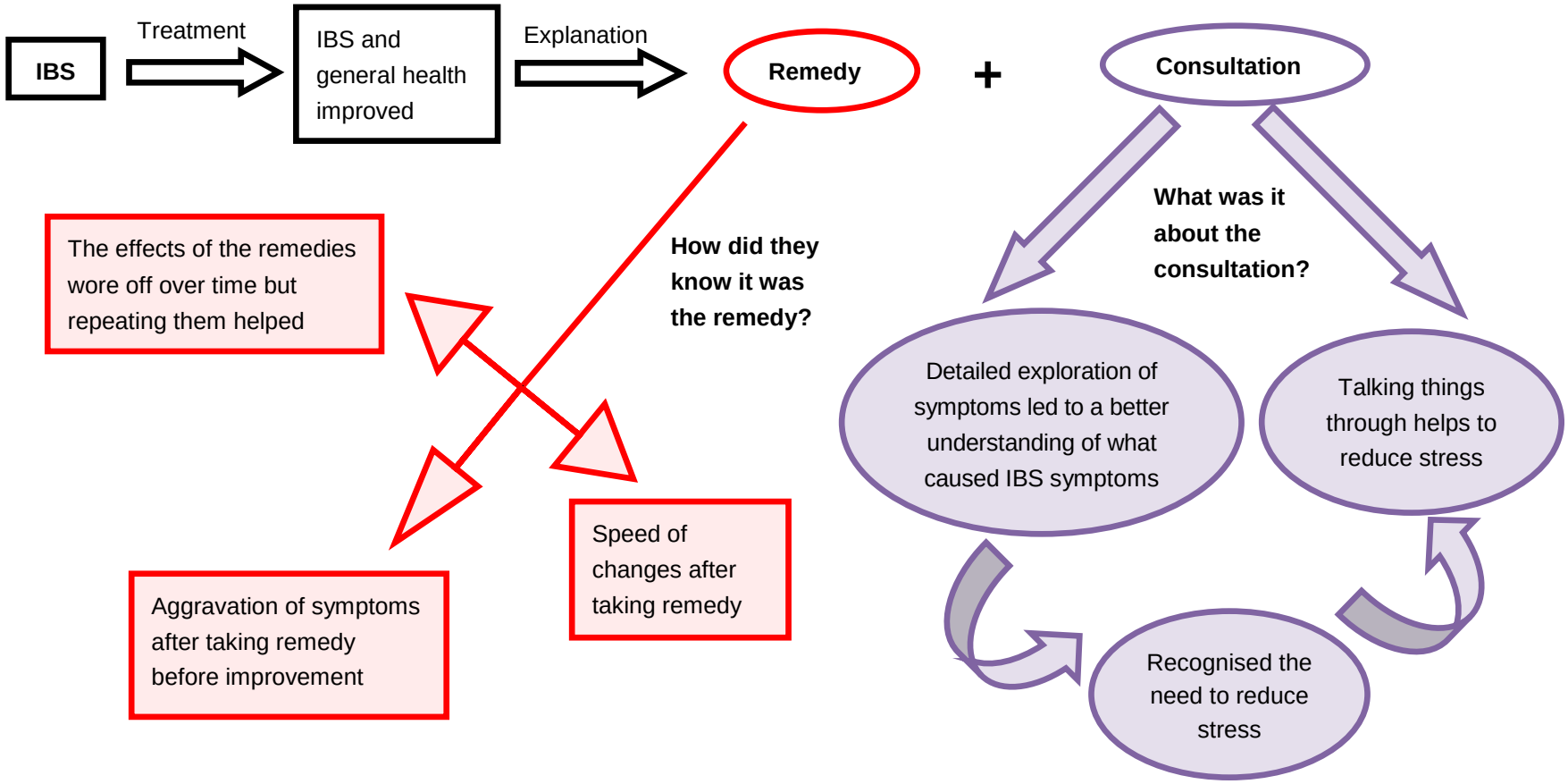

Figure 10-11: Typology four, it was the remedy and the consultation

10.7 Rigor in qualitative research

In the interests of carrying out this study in a rigorous manner, a supervisor was met with to discuss the study throughout the data collection and analysis. The supervisor carried out an independent review of three of the interview transcripts and the initial coding and thoughts and ideas were shared. The supervisor also carried out an independent review of the charting, mapping and typology development, sharing views on where further exploration of the data was warranted. This led to a deeper understanding of the typologies and the patients' individual journeys. In addition this independent analysis increased the likelihood of credibility of the analysis. As a further quality control check, the results of the qualitative analysis were shared with another supervisor who had not been involved in the initial sharing process; this led to further discussion about the data and allowed the data to be explored from an additional view point.

As stated earlier there is no consensus on how best to assess the quality or rigor of qualitative studies. Whilst some authors have published evaluation tools (Long and Godfrey 2004), others have been more cautious about the use of tools and checklists (Barbour 2001). This is because of the potential for checklists to be used prescriptively without thought as to whether fulfilling that check box is appropriate to the study in question. Another more radical position held by extreme relativists is the view that each research study is unique and just as valid in its own right (Mays and Pope 2000). In terms of this PhD study, the view was held that the best way of enabling others to assess the rigor of this study was to be transparent about how the study was conducted and the results analysed, thus allowing other researchers to clearly understand how and why the conclusions were reached. Therefore, in the interests of transparency, the results and how the author came to these results were fully described. The purpose of this is to leave a decision trail, as advocated by Koch (Koch 2006), so that the reader is able to audit for themselves the actions of the researcher. This decision/audit trail has been made clear in the description of the analysis of the results. It is the audit trail that allows the reader to be confident that the results are credible and plausible. Furthermore a description of the population surveyed and the treatment they received has been given to allow future researchers and readers to determine how transferable they believe the data to be (Thomas and Magilvy 2011). The sharing of the data with supervisors, providing a

clear audit trial and description of how these results were arrived at, gives added confidence in the trustworthiness of the analysis process and results of this study. From these processes it can be seen that the results are consistent with the data and how they have been arrived at.

Field notes were made throughout the research process in the form of memos. Some of these were simply to provide an aide memoire after an interview had taken place whereas others contained reflections on the research process. Throughout the study the author was conscious of her dual role as that of a researcher and also as a homeopath. In this PhD the author did not provide any of the IHT. However throughout the duration of the study she was working half a day a month as a professional homeopath providing private healthcare. During the interviews the author did not reveal that she was a homeopath. This was in the belief that patients would be freer to discuss the treatment they had received if they didn't feel that the researcher was aligned to any particular therapy. However had any of the patients asked the researcher about this, she would have given an honest answer. This question was not asked by any of the patients, however one of the therapists did ask at the end of the interview.

The author is aware that her role as a homeopath could lead to a biased view in this study, to minimise the impact of this, she has tried (as far as it is possible), throughout to take the view of the unprejudiced observer. In the homeopathic consultation the homeopaths ideal is to take the stance of the unprejudiced observer. Meaning that, as far as possible, they observe the patient's state without bringing in their own thoughts or ideas. As Kent in his lectures on homeopathic philosophy says "*let me beg of you... to lay aside all that you have heretofore imagined or presumed, the whims and notions, and "what I thought about it,"* page 56 (Kent 1984). To achieve this, the homeopath needs to explore and recognise their own prejudices. The idea being that through knowing their prejudices they work to leave them at the door of the consulting room, during the consultation they seek to understand the patients experience, rather than what the homeopaths thinks the patient is experiencing. Thus the author, as a trained homeopath, has aimed to take the stance of the "unprejudiced observer" when carrying out these interviews. This stance fits with that of the realist perspective as described by Cohen and Crabtree (Cohen and Crabtree 2008). Different authors have described the realist stance in different ways, however Cohen and Crabtree describe it thus, *"we cannot separate ourselves from what we know;*

however, objectivity is an ideal researchers strive for through careful sampling and specific techniques" Page 333 (Cohen and Crabtree 2008). To aid with taking the stance of the "unprejudiced observer," throughout the duration of this study the researcher has reflected on times when she may have been biased and re-assessed actions, whilst thinking have I done this because it is the right thing to do, or have I done it because of a biased standpoint? That is, because I am a homeopath, am I making assumptions about IHT. The quote below from one of the memos demonstrates this process. This memo was made after interviewing one of the homeopaths who had provided IHT.

"This interview was harder than the others because I was trying to be the unprejudiced observer as much as possible and also not start talking in homeopathic terms which would have meant something to the two of us but may not have meant anything to non homeopaths. Through the interviews I have tried to be as unbiased as possible and tried not to lead people in to saying how good homeopathic treatment is. In this interview I was trying very hard to not turn the session into one where we both praised homeopathic treatment, rather I was trying to explore what other things may have led to improvement in people and understand the way this homeopath talked to her patients. All homeopaths are different and I wanted to understand this homeopaths views." Memo made after interviewing Cath, one of the homeopaths.

To enable a deeper analysis of the data both the author and a supervisor read through three transcripts and discussed codes. The purpose was not to agree but to understand where disagreements lay and to understand multiple viewpoints. The idea being that this would facilitate a more through and deeper analysis of the data. Throughout the analysis phase the author and a supervisor met to share ideas and thoughts about the data. Data from the interviews regarding if and how the patients believed their IBS and general health had changed was compared with the patients' questionnaire data from the RCT. Thus qualitative data and quantitative data were compared. This allowed similarities and differences between what the qualitative and quantitative results to be compared. Where there were differences, explanations as to why this should be so were sought from the data. An example of this is the case of Elizabeth who when interviewed said her IBS was significantly better but her IBS-SSS did not back this up. On further exploration of her interview, interviews with the therapist, and

questionnaire data, it was found that she had had a significant change in circumstances shortly after completing treatment and before completing the 26 week questionnaire, which led to depression. Both therapists and patients were interviewed which allowed the therapists views on the treatment to be compared with the patients views, so that, areas of agreement and disagreement could be compared, allowing an overall interpretation to be developed that took into account the views of both the therapists and the patients.

In terms of rigor in qualitative research, Mays and Pope (Mays and Pope 1995) advocate showing how studies fit with other empirical work. Eyles Eyles et al. 2010) has carried out a study looking at homeopaths' perceptions of the homeopathic consultation, described in Chapter 4. The views of participants in this study were compared with the views of homeopaths identified by Eyles to check if there were any areas of overlap. In this study the category "Self realisation" was about making links between the mind and body that lead to realisations about their IBS and themselves. One of the themes identified by Eyles (Eyles *et al.* 2010) in her study on homeopaths views of the homeopathic consultation was that of the consultation allowing the patients to form insights and connections between their symptoms. This connection was thus noted in both this study and Eyles study.

Comparing this study to a study by Brien (Brien, Leydon and Lewith In press) on patient perceptions of the homeopathic consultation, it was noted that participants in both studies found self disclosure in the homeopathic consultation challenging. This theme was found in people from the IHT arm (Sam and Elizabeth) but not found in supportive listening arm. With the patients questioning why the homeopath needed all that information, they felt a bit uncomfortable revealing so much to a stranger, although ultimately they saw a benefit in the downloading.

"I mean like I said at first I really didn't probably appreciate talking about everything. But then afterwards I realised it's a help because of this because of that. At first I felt like not that I was being told off. But it was questioning why do you do that, why do you enjoy doing this. And like things like I love spending time with my family and my nephew and niece I love to be with. Cos we are very close and I've always been there. And done things with them. And I said like you know I try and see the every week or every other week. And well why. I thought because I like to. And I felt like at first does

that mean I'm not meant to like doing that. And it started making me question myself. Like but I think it's just she needs to understand what I do, what I don't do. My emotions are with different scenarios. And then once I start pinning it together I appreciated it more. But again I didn't realise that to begin with why is she was asking me all these questions. I didn't understand that. So I think that put me off, that was what put me off." Sam (IHT)

"I think when you meet somebody for the first time and you start talking about you and in depth about you, your family that's a bit weird at first because you are talking to a complete stranger, who you have never known before. So er, and I suppose I probably am a little bit guarded. So you are a bit like what's all this about you know, I'm sort of thinking what's all this about but hang on this is part of the treatment, then we need to, we need to go with it." Elizabeth (IHT)

Brien (Brien, Leydon and Lewith In press) in her interviews with people who had received IHT for rheumatoid arthritis also found that participants found self disclosure challenging. It is likely that this is due to something specific about the types of questions that are asked by homeopaths to elicit the information required to prescribe a remedy. In this study, although patients could have found self disclosure challenging because IBS can be embarrassing to talk about, Brien's (Brien, Leydon and Lewith In press) study was about rheumatoid arthritis. It is unlikely therefore that the issue around self disclosure is solely related to the condition, but instead, is more generic to IHT.

It is possible that there is a response bias in this sample. All the interviewees reported some benefit. It is unlikely that everyone in the study believed that they had benefitted from the treatment they received because some did not attend all five treatment sessions. When one of the participants in the supportive listening arm was telephoned for her IBS-SSS she said that whilst it was nice to talk to someone she didn't feel it had benefitted. Therefore it is probable that those who did not experience any benefit did not consent to being interviewed. In the letters sent out to participants inviting them to take part in the interviews they were told that the researcher was interested in hearing from people who did and did not experience a benefit from taking part in the study. Everyone who attended at least two consultations was invited to interview therefore everyone who had received treatment was given a chance to take part what ever their experience. However the only patients that agreed to take part in this study were RCT participants who had

completed all their treatment sessions. It is likely that people who completed all their treatment sessions are more likely to have continued with the treatment because they perceived it to be benefitting them. Despite this the study was able to capture a range of views about what it was about the treatment that people had found helpful and why.

This chapter described the results of the qualitative study, explaining each step of the analysis process and how the results of each step informed the analysis of the next step. The end result was the identification of four different typologies that explained what the patients viewed to have been helpful about the treatment they received. The next chapter discusses the results from the systematic review, quantitative and qualitative studies, exploring what the results of these studies mean in terms of the effectiveness of IHT for IBS, in relation to usual care and supportive listening.

11 Discussion

This thesis had two aims: the first was to carry out a systematic review of the effectiveness of homeopathic treatment in the treatment of IBS, and the second was to carry out a trial exploring the effectiveness of IHT in the treatment of IBS. The trial of IHT for IBS had two components: an RCT to explore whether IHT is effective in treating IBS and a qualitative study exploring patients' perspectives of what, if anything, led to any effectiveness of IHT for IBS. This chapter discusses the results of each of the three components of this PhD separately before examining the overall results. The chapter begins with a discussion of the systematic review and the challenges involved with carrying out a systematic review into homeopathic treatment, before reviewing the types of studies identified and their implications in terms of the evidence base of homeopathic treatment.

Following on from the discussion on the systematic review, the methodology and results of the RCT are considered. The use of the cohort multiple RCT (cmRCT) methodology had a significant impact on this study and the reasons for this are explored and their implications examined. The results of the RCT and the outcome measures used are reviewed in light of these factors and conclusions drawn about the information the RCT provided. Following this, the qualitative study and its findings are debated, before moving on to a consideration of the overall outcomes from this study, taking into account the results of all three components. Finally, the strengths and limitations of the study along with areas for future work are discussed.

11.1 Systematic review

The systematic review aimed to assess the evidence of the effectiveness of homeopathic treatment for IBS and to determine whether or not there was a need to conduct a further study to explore the effects of homeopathic treatment for IBS. Therefore the studies identified, the searching process used to identify them, and the information they gave, is discussed in this section. The section begins with a discussion of the searching process.

11.1.1 Searching process and studies identified

No filters were used in the search process. Filters can be used to provide more efficient searches through only identifying a particular type of study

and filtering out all other studies. For example, a search that was only interested in RCTs could use a filter that would only identify RCTs. In this review no filters were used because it was anticipated that only a small number of studies would be identified. In fact only 57 studies were identified without the use of filters. Had filters been employed, fewer studies would have been identified and the issue as to whether or not the filters had been too restrictive would have been of concern. Considering the search terms used in this review, it is possible that the sensitivity of the search could have been improved by using terms of remedies in combination with IBS. However the use of such terms would be difficult as there is no one homeopathic remedy used in the treatment of IBS, rather any of the over 1 000 homeopathic remedies in the materia medica can be used as a treatment for IBS, dependent on the patient's individual symptoms.

In terms of the types of studies identified by the systematic review, there were three RCTs of homeopathic treatment: one case series (Gray 1998) and three audits (Mathie and Robinson 2006; Greeson *et al.* 2008; Thompson *et al.* 2008). However the majority of the studies found in the searches were discussion pieces and case studies. It is unsurprising that case studies were identified, because case studies are commonly used to aid homeopathic prescribing through gaining insights into remedies and how they can be used. The symptoms in the repertory, the book used by homeopaths to match symptoms up to remedies, come from both proving symptoms (symptoms exhibited by a well person who has taken a homeopathic remedy for the purpose of eliciting the symptoms of that remedy), and cured cases. Therefore case studies provide a valuable means for homeopaths to further their knowledge. However the purpose of this work was not to further knowledge on IBS and homoeopathic treatment, it was to evaluate the quality of the evidence that exists for homeopathic treatment being more beneficial than alternative options for care and to potentially estimate the *size* of impact of homeopathic treatment on IBS symptoms. Discussion pieces focused on the symptoms of IBS, the types of remedies that may be appropriate and in some cases on new treatment regimens. One such study is a study by Gamble (Gamble 2008) that discussed the reasoning behind using a particular combination remedy in the treatment of IBS in Australia.

No cohort studies were identified and only three RCTs were identified. There are a variety of reasons as to why only three RCTs were identified, one of

which could be that very few RCTs of homeopathic treatment for IBS are carried out. This is possibly in part due to financial constraints and difficulties in obtaining funding for homeopathic research, meaning that the research focuses on less costly studies. Furthermore it is the opinion of some homeopaths that homeopathic treatment is effective, and research should therefore be conducted into improving practice through gaining a greater understanding of remedies, rather than conducting expensive RCTs. Another reason why so few RCTs were identified could be that trials have been carried out and then have not been published; it can be more difficult for trials with negative results to be published as discussed in Chapter 3. It could also be the case that more trials had been published but not in places where they could be accessed, possibly because they were published in little known journals that are not indexed. Finally, trials could have been published in places where they should have been found, but in fact were not found. In this systematic review measures were taken to maximise the number of studies found as described in Chapter 3, however it is always possible that some RCTs were not identified. Despite the paucity of evidence for homeopathic treatment for IBS, there is a need for the effectiveness of safe non-pharmacological therapies to be evaluated in the treatment of IBS (Manheimer *et al.* 2012). Homeopathic treatment is one such treatment. This systematic review identified two RCTs (Rahlfs and Mossinger 1976; Rahlfs and Mossinger 1979) that compared homeopathic remedies with a placebo remedy in the treatment of IBS. A further RCT that compared homeopathic treatment as an alternative to usual care, to usual care (Owen 1990) was identified. This study was not eligible for inclusion due to the fact that it had not used a global IBS measure as an outcome, rather it asked participants to choose and then score their top four symptoms before and after treatment. The symptoms the participants chose were not reported in the trial and it appeared that the symptoms they chose did not have to be related to their IBS. Owen's study failing to meet the inclusion criteria led to the exclusion of a third of the available evidence. Had the rationale behind Owen's choice of outcome measure been convincing and had Owen's study been of high quality, in terms of how the study had been conducted and reported, it may have been worth considering a retrospective protocol change in order to include Owen's study. However there was no convincing argument as to why Owen had chosen the outcome measure that they had, and no information was given on the symptoms people had

chosen. This meant that the symptoms people chose could have had no relation to IBS, and therefore a retrospective protocol change was not made.

Data from Rahlfs and Mössinger 1976 and Rahlfs and Mössinger 1979 were pooled to give a combined effect size. This showed a statistically significant improvement in global IBS symptoms for homeopathic remedies as compared to a placebo tablet; standardised mean difference 0.56, 95% confidence interval 0.23, 0.90. However, the applicability of these findings are hampered by the poor quality of the reporting of the studies. Consequently, it is impossible to determine whether or not a significant degree of bias exists. The exact details of the randomisation methods were not given in either Rahlfs and Mössinger 1976 (Rahlfs and Mossinger 1976) or Rahlfs and Mössinger 1979 (Rahlfs and Mossinger 1979). However Rahlfs and Mössinger 1979 (Rahlfs and Mossinger 1979) give a clear description of the blinding of participants along with clear details about how the medication was blinded and the steps taken to ensure that participants were not able to determine which arm of the study they were assigned to. This description gives some confidence in the manner in which this study was conducted. However it cannot be certain as to whether or not all aspects of this study were conducted with the same rigour. These studies were carried out before the introduction of the CONSORT guidelines (Schulz *et al.* 2010) which may account for why important information about the flow of participants through the trial is missing. In Rahlfs and Mössinger 1979 (Rahlfs and Mossinger 1979) it is possible that there was some selection bias in terms of deciding to exclude some of the participants from the analysis for not adhering to the protocol, yet including others. The effect of selection bias is that of increasing the effect size and therefore it is possible that the effect size of Rahlfs and Mössinger 1979 (Rahlfs and Mossinger 1979) was inflated.

11.1.2 Implications for practice

In both Rahlfs and Mössinger 1976 (Rahlfs and Mossinger 1976) and Rahlfs and Mössinger 1979 specified homeopathic remedies were used for the treatment of IBS, i.e. these were studies of clinical homeopathy rather than individualised or classical homeopathic treatment. Trials such as Rahlfs and Mössinger 1976 (Rahlfs and Mossinger 1976) and Rahlfs and Mössinger 1979 (Rahlfs and Mossinger 1979) are designed to assess whether or not it is the homeopathic remedy that provides any effectiveness of treatment, rather than any other aspect of homeopathic treatment, such as the

consultation. In the meta-analysis of these two studies a statistically significant effect associated with the homeopathic remedies was found. However due to the low quality of reporting of these studies it cannot be certain as to whether or not these trials were of high quality or not. Therefore it is difficult to assess whether these results would be replicated in everyday practice. Thus it is recommended that Rahlfs and Mössinger's trial (Rahlfs and Mossinger 1976; Rahlfs and Mossinger 1979) is repeated using current reporting guidelines (Schulz *et al.* 2010), to determine whether or not their findings are replicable. Whilst this study would be worth repeating for a European audience, where clinical homeopathy is more prevalent, it could be of less interest to a UK audience where specific remedies for specific conditions are less likely to be used.

In the conclusion the results of the systematic review showed that there was a need for a trial, which was subsequently carried out. The results of this trial are discussed in the next section.

11.2 Randomised controlled trial

11.2.1 Recruitment to the Barnsley Irritable Bowel Syndrome Cohort and the RCT

The study aimed to recruit 198 patients to the RCT, however during the 6 months recruitment phase from January 2011 to June 2011, 115 eligible participants were recruited to Barnsley Irritable Bowel Syndrome Cohort (BIBSC), of these 94 were eligible participants for the RCT. Recruitment was via a questionnaire mailed out to potential participants identified through primary and secondary care. In primary care GP databases were searched for participants who had a diagnosis of IBS or were taking medication for IBS. In secondary care patient records were screened to identify potentially eligible participants. Full details of how participants were recruited are given in Chapter 7. A previous mail out study in Scandinavia achieved a 70% return rate (Hillila, Farkkila and Farkkila 2010), from this it had been anticipated that this study would achieve a 60% return rate (in terms of number of patients who returned the questionnaire), however the actual return rate for this study was between 18-30%, dependent on the GP surgery.

There were a number of reasons for this lower than anticipated recruitment: the difficulty in obtaining agreement from the GP surgeries to carry out the

screening and mail out of questionnaires, the lower than anticipated response rate from those mailed and the differences in how patients were identified by the GP surgeries. Prior to the commencement of the study four GP practices had agreed to identify potential participants for this study. One of these GP surgeries carried out an initial screening of its patients to give an estimate of the number of IBS sufferers within its practice. Using this as a rough guide it was estimated that a sufficient number of IBS patients would be identified by the four GP surgeries who had agreed to take part and the consultant gastroenterologists in secondary care. However the number of patients who actually had IBS was found to be much lower than the initial inspection of the GP database would suggest. This was partly because some of the IBS patients identified were not currently suffering from IBS, and consequently were not eligible to take part in the BIBSC or RCT. In addition to this not all the GP practices coded patients in the same way. One practice in particular appeared to have given diagnosis of IBS for one off incidences of food poisoning and other similar causes of self-limiting diarrhoeal symptoms. This meant that although this particular practice sent out more questionnaires than any of the other practices, only three percent of those who returned questionnaires proved to be eligible for the RCT. Furthermore, although prior to the commencement of the study four GP practices had agreed to taking part, there was a delay in starting the study due to the difficulty in obtaining ethical approval (Chapter 8 outlines these). This meant that by the time the study was ready to start the situation at the GP surgeries had changed and not all of those originally identified were able to recruit patients.

Other studies using the cmRCT methodology have also had a less than expected return rate and it has since been estimated that 15% of those invited to take part in the cohort will take up the offer (Raw 2010). This may be because people are recruited via mailing from GP databases rather than during an appointment that involves a personal contact. It may also be due to the length of the questionnaire or confusion over the consent process (described in 11.2.3). The information on expected return rate, coupled with the recruitment rate achieved in this study, means that to recruit the required number of participants between 8 and 10 GP practices would need to carry out the GP database recruitment alongside the secondary care recruitment.

When it became apparent that there was a possibility that this study would fail to meet its recruitment target, attempts were made to increase the

recruitment rate by contacting additional GPs and asking if they would be able to recruit from their databases. In addition further gastroenterologists were contacted and asked to search their lists; this led to an increase in the recruitment rate but meeting the target still proved to be a problem.

11.2.2 Possible sources of bias in the recruitment process

Whilst GP recruitment aimed to recruit a cross section of the public who suffer from IBS, it is to be questioned as to how representative the sample is. When using a recruitment method based on participants filling out and returning a questionnaire, participants will require a certain level of literacy to be able to complete the questionnaire. Making the questionnaire easy to read and understand, and as simple to complete as possible, will help with this (Edwards *et al.* 2009). However when using outcome measures that consist of a validated questionnaire, the questionnaire that most closely fits with the study and its aims may not be the one that is simplest to complete. Therefore, in the recruitment method used in this study there is a potential conflict when choosing an appropriate outcome questionnaire. Thus, when using questionnaire-based recruitment it is difficult, if not impossible, to prevent the fact that there will be some potentially eligible participants who are not able to complete the questionnaire. It is believed that a potential difficulty with the questionnaire used in this study was the fact that the outcome questionnaires that it was comprised of did not all follow the same format. I.e. the EQ-5D required participants to tick boxes, whilst the IBS-SSS required participants to mark their score on a line scale, whilst the information required for the cost analysis required participants to write numbers in boxes. Working this out could prove too time consuming for some potential participants and may have prevented them from completing the questionnaire. In addition, for this study the participants needed to be screened for IBS prior to being recruited to the BIBSC. Part of the cmRCT methodology involves the identification of potential participants from GP databases and their subsequent assessment for eligibility via a questionnaire to fill in and return (Relton *et al.* 2010). It is almost inevitable with this recruitment method that participants who respond will have a certain level of comprehension, which means that some members of the population will be excluded. The reading ease of the initial questionnaire was found to be 79.8%, when tested with the Flesch Reading Ease test, (the higher the percentage the easier the document is to read), this score indicates that the document was fairly easy to read (Flesch 1948). However,

as already discussed, the fact that the questionnaire comprised of various outcome questionnaires, each requiring different responses, could have led to confusion, resulting in difficulty in completing the questionnaire. Furthermore only people who visit their GP with IBS symptoms will have been identified as potentially eligible. It is possible that there are people within the population who suffer with IBS but have never visited their GP about their symptoms (Jones 2008). In addition, it is likely that there will people who are able to read and understand the questionnaire but are not interested in taking part in the study, or do not want the hassle of having to fill in a questionnaire. Trying to make the questionnaire as short and simple as possible reduces the burden on potential participants. In theory more people would complete a shorter simpler questionnaire than would complete a long complex questionnaire. In this study an association was found between failure to complete the 26 week questionnaire and being in employment. This meant that people who were employed were less likely to complete the 26 week questionnaire, compared to those who were not employed. In order to maximise the return rate of the 26 week questionnaire, systematic reviews of how to increase return rates of questionnaires were accessed (Edwards *et al.* 2002; Nakash *et al.* 2006) and where possible measures that had been found to be beneficial were taken, such as handwriting the participants name, using proper stamps and using a University of Leeds header on the questionnaires and accompanying letters.

Although the recruitment method used in this study aimed to recruit a cross-section of people with IBS in the community, it will, by its nature, have failed to include some sections of the population with IBS. This means that the people included will not be truly representative of the general population with IBS living in the Barnsley area. It was observed that fewer men returned the questionnaire than women, however, although the total number of questionnaires sent out is known, the GP surgeries were not able to give a breakdown by sex of the questionnaires they sent out. This means that it is unknown as to whether or not a greater percentage of women returned their questionnaires compared to men. However IBS is more prevalent in women than men (Smith *et al.* 2004), in Smith et al's cross sectional observation survey 84% of the subjects were women. The greater prevalence of IBS in women may account for fewer of the returned questionnaires being from men. In the randomisation process no men were randomised to IHT, this was a chance occurrence that may have had an impact on the results. It is

possible that men would have had a different view of IHT and possibly have had different results to women. The lack of men in the IHT arm could therefore have introduced a bias into the study in terms of the results of the IHT arm, however the fact that there are fewer men in the study overall is considered to replicate the real world. It may have been beneficial to stratify randomisation by gender, which would have ensured that some men would have been randomised to IHT. This would be worth considering in any future studies.

11.2.3 Administration of the BIBSC

The cmRCT design is a new design, which means that necessarily there will be developments in the way in which it is implemented. The observations of this study may be important in future developments of the cmRCT design. In particular studying some of the difficulties associated with the administration of BIBSC may prove useful in refining the cmRCT design. In this study, the cmRCT methodology was complicated to manage. This was because there proved to be multiple levels of consent, which hadn't been anticipated prior to commencement of the study. On the face of it the consent process was seemingly simple, with participants having the option to consent to one or all of three separate options: the data they supplied being used, to be contacted again and for the study team to look at their medical records. Yet in practice this consent process was complex to interpret. This complexity led to a considerable amount of time being needed to assess what participants had consented to, and what obligations had been made to the participants in terms of sending them future questionnaires. Additionally recruitment to the RCT was a two stage process: first participants were screened for eligibility to the BIBSC and then if eligible they were screened for eligibility to the RCT. One of the eligibility criteria for the BIBSC was to meet the Rome III criteria for IBS and one of the eligibility criteria for the RCT was to score over 100 on the IBS-SSS. It was found that, although some people did not meet the Rome III criteria, they did score over 100 on the IBS-SSS. This highlights the discrepancy between different measures and the difficulty in making a diagnosis in conditions such as IBS, where its presence is not determined through a physical test (Talley and Spiller 2002).

In this study there were six levels of consent and eligibility:

Group 1: consented and eligible for both RCT and BIBSC

Group 2: consented and eligible for BIBSC

Group 3: consented but not eligible for BIBSC or RCT

Group 4: did not consent to be contacted again

Group 5: did not consent to use of data or be contacted again, therefore nothing could be done.

Group 6: did not consent to use of data but consented to be contacted again.

People in group three, i.e. those who had consented, but were not eligible to take part in the BIBSC study, needed to continue to be sent questionnaires. This was because there was no mechanism by which participants were told whether or not they were eligible for the BIBSC study, thus everyone who had consented would be expecting to receive future questionnaires. However the purpose of collecting data on these people has to be questioned, especially with respect to whether or not this data will be used in any way. If the data is not used then the ethics of collecting data from these people has be explored. In the initial patient information sheet and invitation letter everyone was told that if they consented to take part in the study they would be sent questionnaires at various time frames. This meant that everyone who consented to take part in the study would be expecting further questionnaires, unless they were informed that they were not eligible to take part in the study, in which case they would not be sent any further questionnaires. However as it stands the cmRCT design continues to collect data from all those who return their questionnaire, regardless of whether or not they are eligible for the BIBSC study. Thus there is an ethical dilemma as to what to do with these people. Is it more ethical to carry on sending them questionnaires and not use the data, or is it more ethical to stop sending them questionnaires. Along with the question of ethics, there are cost implications associated with sending questionnaires out to people whose data cannot be included in the study. This is an important issue and one that needs to be considered both in terms of ethical and financial considerations. For the future it would be useful to carry out a study exploring how patients understand the consent process employed in this study, and from this, identify how it could be simplified.

In addition to the ethical and financial issue of people in group three, there is the issue of those in group six. These people failed to consent to the use of the data that they had provided, however they did consent to be contacted again. The data from these participants could not be used, but like those in group three there was the obligation to continue to send these participants

questionnaires. The failure to consent to the use of the data was thought to be either due to an error on their part, or a lack of understanding of how the data would be used. This is because it seems contradictory to go to the trouble of filling out a questionnaire and then failing to allow its contents to be used.

In summary there were six levels of eligibility and consent for this study, which made the BIBSC and the RCT complicated to administer and maintain. This means that using the cmRCT methodology in a small scale study with limited finances is not simple. It would have been less complex to use an already established cohort, assess for eligibility and then randomly select, rather than set up a cohort at the same time as conducting the study. This would become feasible if the cmRCT model became widely established and thus more cohorts available to recruit from. Alternatively, the complexity of the cmRCT design may not have been necessary; the more usual way of addressing simple questions such as that posed in this study is to follow a straightforward parallel randomised controlled trial design. In this case the GP could mail out the questionnaire; potential participants would be given a phone number to call if they were interested in taking part in the study. Those who called the number could then have been screened over the phone using the Rome III criteria, and if found to be eligible sent a shorter questionnaire to fill in. It is also possible that the cmRCT design could be modified so that the GP's mail out the questionnaire and a pre-screening process is employed as described above. This would lead to people who are not eligible for the cohort being screened out in the initial stage, thus removing the problem of the obligation to continue sending questionnaires to people who are not eligible to take part in the cohort. Whilst this is feasible for a small scale study such as that conducted in this PhD, if a large scale cohort of thousands of people was desired, then people phoning for their eligibility to be assessed may not prove to be feasible.

11.2.4 Uptake of offer of treatment

Those randomly selected to be offered IHT or supportive listening were sent an invitation letter, participant information sheet and consent form to sign and return. Participants were telephoned a week after posting the letters to ensure that they had received the letter. All participants were telephoned unless they had already returned a signed consent form.

A difference was found between the uptake of treatment between the two arms, with fewer participants taking up the offer of supportive listening (50%), than those taking up the offer of IHT (75%). The reason for this is unclear, because it was a positive opt-in to treatment there was no mechanism by which reasons for failing to uptake the offer were routinely sought. Where possible, participants were asked for reasons, however due to the low numbers, diversity of replies and possibility of participants not wishing to divulge the reason for not taking up the offer, no overall theory as to why this difference occurred could be made. Furthermore because of the small numbers of participants in both groups, what appears to be a large difference in the uptake between the two groups may simply be due to chance. Despite this, it is possible that more people may have taken up the offer of IHT because it was easier to see how IHT may help, whereas for supportive listening it was less obvious to see how it would help. Paula, who took up the offer of supportive listening, was initially sceptical of how it may help.

"I must admit that at first when I read it I thought whatever's talking about it going to do, an how ridiculous, and I thought no, just try, just fill it in and try." Paula (patient, supportive listening)

If adhering to the cmRCT methodology in its strictest form, when participants are recruited to the cohort, no mention is made about any treatments that may be offered. Participants are purely recruited to join an observational cohort. Only those randomly selected to be offered a treatment are told about the treatment that they are being offered; they are not told about any other treatments that other participants may be receiving. However due to the research ethics committees concerns about this model, in the letter inviting people to take part in the BIBSC study, a brief mention was made about the fact that they may be offered a treatment. The treatments that may be offered were not described in great detail and participants would have had to have read the participant information sheet to realise that there was the possibility of receiving a treatment. The text included in the BIBSC participant information sheet was;

"About 1 in 20 people who have chosen to participate in this study will be randomly selected to be offered a treatment. We currently want to test the effectiveness of the following two treatments:

1. Homeopathic treatment

2. Supportive listening

*Inclusion in the study **does not necessarily mean** that you will be offered one of the above treatments. If you are randomly selected to be offered one of the treatments you will be sent a separate letter and an information sheet with further details describing the treatment offered."*

It is possible then, that the participants did not return the study questionnaire expecting to be offered a treatment and were not treatment seekers, rather they had other reasons for returning the questionnaire, such as wanting to help others with IBS. This may have led to a lower uptake of the treatment options than would have been the case if people had enrolled in the study with the express desire to receive a treatment. However this does not explain why less people took up the offer of supportive listening than took up the offer of IHT.

To reduce the problem of participants not taking up the offer of treatment, a question could have been included in the initial questionnaire that gave a list of treatments, and people asked to tick any treatment that they would be interested in receiving. One of the exclusion criteria for the RCT could then be - not being interested in homeopathic treatment and supportive listening. This would reduce the problem of people not being interested in the treatment they were offered. However people who stated that they were interested in homeopathic treatment and supportive listening may be systematically different from those who didn't state that they were interested. This may reduce the generalisability of the results. In addition offering people a list of treatments to tick may lead to people being disappointed if they weren't offered a treatment, leading to resentful demoralisation, one of the problems that the cmRCT was designed to avoid.

The homeopaths and counsellors who provided the treatments found that even when people had returned their signed consent form, some people were not able to attend appointments. This was a particular problem for those who worked and were unable to get time off work to take part in the study. One of the homeopaths noted that in a previous study on homeopathy for fibromyalgia, a significant number of the participants were unable to work. This was due to being too ill, which resulted in these people being more able to attend appointments. It may also be that due to the nature of IBS; some participants may not have wanted to approach their employer for time off work. One participant from the supportive listening arm, who took

part in the qualitative interviews, described a situation when she had felt ill at work.

" Er you can't keep nipping to the loo, with all these fellers and I don't want to say anything, erm and I thought, and I did take something and I did, I did manage but if I'd started not to manage at work, I'd have told I was sick or something, I wouldn't have told em that (I had IBS)." Paula (patient, supportive listening)

This illustrates the reluctance some people have about telling their workplace that they have IBS. Therefore there were potential barriers to people accepting the offer of treatment. It is likely that these barriers were similar across both treatment groups and does not explain why the uptake should be lower in the supportive listening arm. It is possible that people thought that supportive listening would not help them and therefore were less keen to take up the offer, but this is not certain.

The expectation of benefit and credibility of the treatments to participants was assessed using a scale developed by Borkovec and Nau (Borkovec and Nau 1972) and modified for IBS, by Drossman (Drossman *et al.* 2003). It was intended that all participants in the supportive listening and IHT arms would be given this questionnaire at their second appointment. However this measure was not consistently applied across the two treatment groups. All twelve people who received IHT returned the credibility questionnaire, yet only five of the nine people who received supportive listening returned their questionnaire. This discrepancy may in part be due to the different attitudes of the therapists providing the treatments. The counsellors who provided the supportive listening expressed concerns about the credibility of the questionnaire, in that they did not agree with the content of the questions. In particular they did not like the use of the word logical in the question, "How logical does this type of treatment seem to you for helping functional bowel symptoms?" It could therefore be that not all participants in the supportive listening arm were given the form by the counsellors, or the counsellors portrayed the form in a negative light when giving it to the participants, (possibly reducing the desire of the participants to fill out the form), or the participants did not return the form for another reason.

Furthermore it could have been that the counsellors were unable to disguise their strong feelings about the content of this questionnaire, and this in some way affected the participants desire to complete the questionnaire. One of

the counsellors reported that the participants did not understand the questions; however this is surprising as none of the people in the IHT arm appeared to have had any difficulties with the questions. To prevent the possibility of therapists having an undue influence over the return of the expectation of benefit questionnaire it would have been prudent to have posted the questionnaires out to the participants, rather than relying on the therapists to give them out.

The rationale for giving out the questionnaires at the second appointment was to assess how credible the participants found the treatment they were receiving once they had had some experience of the treatment. However it may also have been useful to post a copy of the expectation of benefit questionnaire with the offer of treatment letter. If participants then returned the expectation of treatment questionnaire regardless of whether they took up the offer, information may have been gained as to why less people took up the offer of supportive listening than took up the offer of IHT. It is of course possible that those not interested in taking up the offer of treatment would not have returned the form anyway but without trying it this is unknown.

11.2.5 Attendance at appointments

All twelve people (100%) who took up the offer of IHT attended all five appointments whilst five of the nine people (55.6%) who took up the offer of supportive listening attended all five appointments. The reasons for this difference are unknown. Furthermore, due to the small numbers in both arms of this study, all conclusions about the apparent differences in response rate and attendance rate are tentative. It could be that those in the IHT arm felt a benefit from the treatment and therefore continued with it, whilst some of those in the listening arm decided not to carry on with treatment because they did not feel a benefit. It could also have been that those in the supportive listening arm did not like the treatment, but this is not clear. Fewer people randomised to the supportive listening arm returned their 26 week questionnaires (12 out of 18) compared to those randomised to IHT (15 out of 16), which suggests that there was something different about the IHT arm compared to the supportive listening arm, although the exact nature of this difference is not certain. This differential return rate is discussed in further detail in Section 11.2.8. One thing that could have affected this is the therapists themselves. Their potential impact is discussed in the next section.

11.2.6 Impact of who delivered the treatment

Due to concerns expressed by the research ethics committee, trained counsellors delivered the supportive listening rather than someone trained in basic listening skills. In this study, prior to applying for ethical approval, attempts had been made to identify nurses working at Barnsley Hospital who had been trained in basic listening skills, and who may have been able to deliver the supportive listening. Due to the fact that no suitable practitioners were found, it was felt that the best option was to have trained counsellors delivering the supportive listening, as the research ethics committee advised. This could have led to the provision of an enhanced supportive listening because the counsellors are likely to have a greater knowledge of counselling skills than someone trained in basic listening skills. To address this the counsellors were specifically asked to provide supportive listening rather than counselling, however it is possible that the counsellors provided a form of counselling rather than supportive listening. As a check, it had been intended that a researcher at University of Leeds would assess a random selection of listening sessions, as described in Chapter 6. However it was not possible to identify an appropriate researcher within the time scales of this study. This check would have allowed an assessment to be made as to whether or not supportive listening or a more advanced form of counselling was being delivered.

Another potential issue was the fact that the homeopaths were providing “their” treatment as they would deliver it in everyday practice. Yet the counsellors providing supportive listening were not providing “their” treatment as they would deliver it in everyday practice, both being person centred counsellors who would normally use a variety of techniques in their normal practice. It could therefore have been the case that the counsellors providing the supportive listening may not have had the same level of affinity with supportive listening as the homeopaths had with IHT. This could have led to an unconscious belief in the counsellors that supportive listening would not help the participants, which could in some way have been conveyed to the participants. This is merely supposition, however it is a possibility that is worth considering. Furthermore the homeopaths had been involved in the project from its inception and the idea of assessing IHT for IBS had, in part, been their idea. Therefore there was the potential for the homeopaths to have a greater affinity with the study than the counsellors, who were recruited to the trial once ethical approval had been received from

the research ethics committee. A greater affinity with the trial may have led to greater enthusiasm for the trial, which could in some way been conveyed to the participants, thus providing them with added impetus for remaining in the trial and returning questionnaires, which may in part explain the differential return rate.

None of this can be certain; however what can be concluded is that IHT was more acceptable to patients in this trial that supportive listening was. The reasons for this are unclear but could be related to some of the points discussed above such as: the credibility of the treatment, or the enthusiasm of the therapist providing the treatment. However the possibility that this was merely due to chance cannot be ignored.

11.2.7 Impact of recruitment on results

As already stated the recruitment was lower than anticipated. To put the lower recruitment into context, the power of the t-test between usual care and IHT was calculated retrospectively to determine what the actual power of the study was for this comparison. As with the power calculations carried out prior to the commencement of the study, this was calculated in PS Power (Dupont and Plummer 2009). The calculation was based on 16 people in the IHT arm and 60 in the usual care arm, with a standard deviation 85, alpha of 0.05 and difference of 50 points.

PS Power gave the power as 0.539.Therefore the actual power to detect a difference between IHT and usual care for this study was 54%, lower than the 80% that was desired. This shows that the study was underpowered to detect a clinically relevant difference between IHT and usual care.

A further calculation was carried out to determine the power of the study to detect a difference between IHT and supportive listening. This calculation was based on 16 participants in the IHT arm and 18 in the supportive listening arm, with a standard deviation of 85, alpha of 0.05 and a clinically relevant difference of 50 points.

The power was calculated to be 0.374.Therefore the power was 37%. This is low. In retrospect using a 4:1:1 ratio of usual care: IHT: supportive listening and powering the study to detect a difference between usual care and IHT may not have been the optimum use of resources. Had the same number of people been recruited, but the recruitment spread evenly across four arms, then the power would have been 0.623, i.e. 62.3%. This was calculated based on 31 people in each of the three arms, a standard deviation of 85,

alpha of 0.05 and a clinically relevant difference of 50 points. This would have resulted in a higher power than was achieved in this study. However as there were not sufficient funds available to carry out a fully powered trial with equal numbers of participants in each arm, the study was not set up for equal numbers in each arm. It is to be debated as to whether or not using the unequal randomisation was the best thing to do. If the intention is to recruit a large cohort of people which is then used for multiple RCTs, as the cmRCT methodology intends, then the use of unequal randomisation is based on sound principles, in terms of cost and the best use of resources. However with this study there was no large cohort to randomise from and insufficient funding to recruit and maintain a large cohort of people with IBS. Therefore in retrospect for this particular study it may have been of more benefit to use a 1:1:1 ratio. However it should be borne in mind that whatever the ratio that had been used the trial would have under-recruited and therefore been underpowered. The issue with an underpowered trial is the fact that it may find no significant benefit of the experimental treatment over the control treatment when in reality there is a difference, i.e. a false negative. Whilst it has been said that underpowered trials are unethical because they cannot answer the question they set out to address (Halpern, Karlawish and Berlin 2002), it cannot be guaranteed that a trial will recruit the desired number of people. However it is important that steps are taken to minimise the chance of under recruitment. In this trial the recruitment rate was estimated prior to conducting the study and GPs approached in advance as discussed in 11.2.1. This led to an assessment being made as to whether it was feasible to recruit the required number of participants before carrying out the study. This was done to minimise the chances of the study being underpowered.

Despite this study being underpowered, it is still able to make a contribution to the evidence base of homeopathic treatment for IBS. Rahlfs and Mössinger 1976 (Rahlfs and Mossinger 1976) and Rahlfs and Mössinger 1979 (Rahlfs and Mossinger 1979) recruited 72 and 119 participants respectively; this study is a similar size, and makes a modest contribution to the body of evidence for homeopathic treatment in the treatment of IBS. This study also contributes to the knowledge of the use of the cmRCT design in practice, as discussed in Section 11.2.3.

11.2.8 Return rate of questionnaire

Over all three arms, after one questionnaire and one reminder were sent out, the return rate for the 26 week questionnaire was 81.9 %. Given the low return rate for the initial questionnaire, this was a surprisingly high number. However a prospective cohort study assessing development of IBS (Spence and Moss-Morris 2007) experienced similar findings with a relatively low return rate of the initial questionnaire (52%) followed by a good response to a follow up questionnaire (94%). This leads to the belief that once people had decided to take part in a study such as the BIBSC study, they are committed to returning their questionnaires. Nonetheless there were differences between the arms in terms of return rate, 85% of those in usual care returned their 26 week questionnaire, 93.75% of those in IHT arm and 61.11% in supportive listening arm. The low return rate in the supportive listening arm compared to the other two arms was particularly worrying, as this may have resulted in a bias in the results of the trial. This could have been either an overestimate of the effect of supportive listening, if only those that found the treatment effective returned their questionnaires, or an under estimation of the effectiveness of supportive listening, if those who didn't return their questionnaires all felt better. Without knowing the reasons for non-return of the questionnaire this could not be known. Consequently to further increase the response rate, those who didn't return their questionnaire were telephoned to ask if they would give their score for the IBS-SSS score over the phone. This action increased the return rate of IBS-SS scores to 90.4%, broken down as follows: 90% in usual care arm, 100% in the IHT arm and 83.3% in supportive listening arm. Despite the differences in the return rate for IBS-SSS after phone calls, when the analysis of missing data was carried out as described in Chapter 9, allocation was not found to be a significant predictor as to whether IBS-SSS was missing. Whether or not allocation was a significant predictor of missing IBS-SSS prior to the telephone calls is not known because this was not tested in the missing data analysis. The reason for this was the desire not to over test the data as explained in Chapter 7, and in order to decide how to deal with the missing data it was more important to explore whether there were any predictors of missingness of IBS-SSS after the phone calls.

Summing up all the facts about: recruitment rate, take up of offer of treatment, attendance of appointments and return rate of questionnaires, there appears to have been something different about IHT compared to

supportive listening, in terms of its acceptability to participants. Compared to IHT, a lower percentage of people took up the offer of supportive listening, a lower percentage of people attended all five treatment appointments and a lower percentage of people returned their 26 week questionnaire. Why this should be so remains unclear, as discussed in Section 11.2.4; it may have been related to the counsellors who provided the supportive listening being less enthusiastic and having less affinity for the trial, yet this does not explain the differential acceptance of offer of treatment as the counsellors had not had any contact with the participants at this point. Therefore although it can be concluded that IHT was more acceptable to participants, why this should be so is at this point unknown. It could be that as already discussed it was easier for participants to perceive how IHT may help them. It would be useful if any future trials of IHT compared to supportive listening are carried out, that they incorporate a means for routinely asking participants why they have not taken up the offer of treatment. However this may be ethically difficult as it has the potential to put the participants in an uncomfortable situation, in which they may not feel able or willing to tell the truth.

To test the sensitivity of the results, the missing IBS-SSS data was inputted assuming best and worst case scenarios i.e. the maximum IBS-SSS was inputted for all the people for whom there was missing 26 week IBS-SSS (worst case) and the minimum IBS-SSS was inputted for all the people for whom there was missing 26 week IBS-SSS (best case). An ANCOVA was conducted for each of these scenarios. As was calculated in Chapter 9, the independent variable was allocation which had three levels; usual care, IHT and supportive listening. The dependent variable was change in IBS-SSS. The covariates were age, employment status and initial IBS-SSS. Assuming the worst case scenario led to the difference between the groups associated with allocation just being statistically significant, $F(2,82) = 3.14$ $p = 0.049$ $\eta^2 = 0.71$. Whereas when assuming a best case scenario, no statistically significant difference was found between the groups, $F(2,82) = 0.089$ $p = 0.915$ $\eta^2 = 0.02$. This indicates that whilst the results are sensitive to the worst case scenario, even in the worst case scenario the difference between the groups is only just significant. Therefore it can be concluded that the missing IBS-SSS data is unlikely to have made a significant change in the results.

11.3 What the results of the RCT mean

11.3.1 IBS-SSS

The primary outcome was the change in IBS-SSS between baseline and 26 weeks. T-tests were carried out to compare IHT to usual care and IHT to supportive listening. An ANCOVA adjusting for age, employment status and initial IBS-SSS was also carried out.

Although the change in IBS-SSS was greater for the IHT arm, the spread of data for change in IBS-SS was large; at least 300 points for all three arms. I.e. some people experienced an improvement of over 200 points while others worsened by over 100 points. This shows that people's reactions in terms of change in their IBS symptoms were not homogenous, this lack of homogeneity in reactions was true across all arms.

The results for the ANCOVA and the t-tests were not in agreement, with the ANCOVA test finding no differences according to allocation. i.e. there were no differences in the groups. However the results from the Student's t-tests indicated that there was a statistically significant difference between IHT and usual care but not between homoeopathic treatment and supportive listening. This illustrates how it is possible for different tests to give different answers. Furthermore it also demonstrates the importance of stating upfront what the primary test method and comparison will be to prevent intentional or unintentional use of the result which best fits the investigators theory. In this study the primary comparison was the comparison of IHT with supportive listening using a Student's T-test, in which no statistically significant differences were found.

The results of the ANCOVA are contradictory to the views of Ernst and Lee (Ernst and Lee, 2008), that pragmatic trials of homeopathic treatment compared to usual care are bound to find a positive result. The results of this PhD study indicate that it is possible that pragmatic trials do not always find a positive result. However this study was underpowered and therefore it cannot be known whether or not this result would be replicated in a fully powered trial.

In relation to the results of the RCT it must be borne in mind that the study was underpowered to detect a difference which means that the study is at risk of a type II error, where no difference is found when a difference really exists. The lack of power of the study may be why no difference was

detected between IHT and supportive listening, or it may be that there is genuinely no difference between the two treatments. It could also be that the intervention only works in a selected sub-group of people and not the rest of the population studied, i.e. there are responders and non-responders. If this was the case the effectiveness of the intervention in the responders would swamped by its lack of effectiveness in the non-responders, with the average effect not being applicable to either the responders or the non-responders. Without carrying out a further fully powered RCT comparing IHT and supportive listening it cannot be known whether or not the failure to identify a statistically significant difference was due to the study being underpowered. It could also be the case that the counsellors delivered counselling rather than supportive listening and this led to a greater effectiveness of the supportive listening because it wasn't actually supportive listening that was being delivered, as already discussed in Section 11.2.6.

In exploring the IBS-SSS and what the scores say about the three treatments it is of interest to look at the results depicting the percentage of people in each arm who achieved a clinically relevant improvement or deterioration. In all three arms the percentage of people who deteriorated to a clinically relevant degree was similar with 18.3% of those in the usual care arm; 18.8% of those in the IHT arm and 16.7% of those in the supportive listening arm experiencing a clinically relevant deterioration. This indicates that having one of the treatments in this study appears not to have a protective effect in terms of preventing people from deteriorating to a clinically relevant degree. It therefore appears that neither IHT nor supportive listening provide a means of preventing some people from getting significantly worse. Whether this tells us more about the nature of IBS or more about the treatments on offer is unclear at this point.

However in terms of the percentages of people who improved to a clinically significant level there appeared to be a difference between the groups; with 62.5% of those in the IHT arm improving to a clinically significant level, 38.9% of those in the supportive listening arm and 25% of those in the usual care arm. This data was compared but no formal statistical tests were carried out to prevent over testing of the data as explained in Chapter 7. The large difference between the IHT and supportive listening and usual care arms is of interest. It may be that because fewer people took up the offer of supportive listening and less people attended all five appointments, a lower percentage in the supportive listening arm achieved a clinically relevant

change. Or it could be that because people weren't seeing an improvement they did not carry on attending the supportive listening appointments; this is not known. These results again highlight the importance of deciding in advance what are going to be the outcome measures and tests carried out.

11.3.2 Hospital anxiety and depression scores (HADS)

In terms of HADS the mean change indicated an improvement for all three arms, but this change was minimal in the IHT and supportive listening arms, where the mean change was -0.2 and -0.18 respectively. The change in HADS between baseline and 26 weeks was compared for usual care and IHT, and IHT and supportive listening using t-tests. The change in HADS between baseline and 26 weeks was also compared across all three arms using ANCOVA adjusted for age, employment status and initial IBS-SSS. No differences were found between any of the comparisons, t-tests or ANCOVA. There were a high number of people who were experiencing anxiety and/or depression in this study, this is to be expected, as a link between IBS and depression has already been reported (Ten Berg *et al.* 2006). Contrary to expectation though was the finding that although the mean change in IBS-SSS in the IHT arm indicated a clinically relevant change in IBS-SSS, there was only a minimal improvement in HADS. Given the link between IBS and anxiety and depression it would be expected that an improvement in IBS-SSS would be accompanied by an improvement in HADS. However a study exploring the impact of physical activity on IBS also found that although physical activity led to an improvement in gastrointestinal symptoms it did not lead to an improvement in symptoms of anxiety and depression (Morlin *et al.* 2008). This suggests that the link between IBS and anxiety and depression is complex. It is hard to know whether anxiety and depression causes IBS, whether anxiety and depression is a manifestation of IBS, whether anxiety and depression in IBS patients results from their having IBS, or a mixture of two or more of the above.

11.3.3 CARE measure

In terms of empathy of practitioner, the median score (Inter quartile range) for IHT 50.0 (33.00-50.00) compared to 43.50 (41.50-48.50) for the supportive listening arm. However due to the low number of people who returned this form and the lower than anticipated recruitment rate it was not possible to explore any correlations between CARE scores and outcome, as

discussed in Chapter 9. It had been thought that use of the CARE measure would provide an insight into how people viewed the therapist they saw, along with the possibility of determining whether or not there was a correlation between outcome and how the practitioners were viewed. Although participants were asked in the qualitative interviews about the practitioners, not everybody who attended treatment was interviewed; furthermore it is considered that it would be easier for a participant to rate the therapist in a negative light in a questionnaire completed in their own home compared to in an interview with a researcher (Fisher 1993).

11.3.4 EQ-5D

In the EQ-5D domains, of the people that responded there were fewer people who had *no problems* at 26 weeks than had no problems at baseline. This is contrary to what would be expected. This was true for all domains in the usual care and supportive listening arms. However in the IHT arm in the domains of mobility and pain, a greater number of people said they had no problems at 26 weeks than said they had no problems at baseline. In the IHT arm, in the domain of self-care, the number of people who experienced no problems was the same at 26 weeks as it was at baseline.

It would have been expected that had people's overall health improved, there would be a greater number of people reporting no problems after 26 weeks, compared to baseline. As IHT aims to treat the "whole person" it would be expected that if the treatment was effective it would not just lead to a benefit in terms of IBS symptoms but also a benefit in terms of any other health complaints and an improvement in overall wellbeing. The fact that it is only in the IHT arm that even the same number of people are reporting no problems at 26 weeks indicates that it is possible that IHT may have in some way improved other areas aside from IBS. Despite this the HADS for those in the IHT arm did not indicate a particular benefit of IHT in terms of reduction of anxiety and depression.

The fact that fewer people in the usual care and supportive listening arms were experiencing no problems in all domains at 26 weeks compared to baseline could in part be due to the amount of missing data. However even if everyone with missing data had reported no problems, this still would not have led to a greater or even the same number of people reporting no problems at 26 weeks, compared to baseline, across all domains. Therefore it remains unclear as to why fewer people should be reporting no problems

at 26 weeks compared to baseline, especially in light of the EQ-5D VAS results.

In terms of the EQ-5D VAS in all arms, the mean score had increased, with those in the IHT arm having increased the most. An increase in score indicates an improvement in overall health state. This is in contrast to the domains, where in the supportive listening arm it appeared on average that people were the same or had worsened. The results of the EQ-5D therefore are supplying a contradictory message.

11.3.5 Conclusions from the randomised controlled trial

The mean change in IBS-SSS indicated an improvement across all arms of the trial whether participants received a treatment or not. Those in the IHT experienced the greatest mean improvement, then those in the supportive listening arm, then those in the usual care arm. It could be that some of these improvements can be explained by regression to the mean, whereby participants who completed the baseline questionnaire did so at a time when their IBS symptoms were at their worst and thus IBS was on their minds, leading to them deciding to take part in the study. Such people are likely to improve anyway due to the cyclical nature of IBS, whereas those who didn't complete the questionnaire may have decided not to complete it because they didn't have any IBS symptoms at that time. There could also be some improvement due to the Hawthorn effect where people improve simply through the action of being involved in a trial. Mike, in the supportive listening arm, was proud to be involved in a trial where his experiences could be of benefit to other people.

"And also what's always given me a bit of pride in what I'm doing is helping other people. You know what I mean and that's summat important to me, I aint selfish I've never been a selfish person…You know what I mean and she (the counsellor) says thank you for doing this and I'm no anytime cos if it doesn't help me it might help somebody else and that's how I've thought of it all the way along." Mike (patient, supportive listening)

The treatment may or may not have had an effect. Yet it is possible that feeling proud of doing something that could help others may have been beneficial and have led to an improvement in symptoms.

Although no significant differences were found apart from in a t-test between usual care and IHT, this may be because the study was underpowered i.e. due to a type II error where IHT was more effective than supportive listening,

but the study failed to detect that. It could also be that the intervention only works in a selected sub-group of people and not the rest of the population studied, hence the effect is diluted.

What can be concluded from these results however is that IHT is more acceptable to the population studied than supportive listening. This conclusion has been drawn from the fact that a greater percentage of people took up the offer of IHT and a greater number attended all five appointments. It is possible that if a different population was studied then a different result may be found. Possibly in a population that had more of an affinity with counselling.

11.4 The inclusion of the results from this PhD study in the systematic review

This PhD study met the eligibility criteria for inclusion into the systematic review as described in Chapter 3. Therefore the results from the systematic review were reanalysed with the addition of the results from this study. Comparing this study with Rahlfs and Mössinger 1976 (Rahlfs and Mossinger 1976) and Rahlfs and Mössinger 1979 (Rahlfs and Mossinger 1979), all three studies assessed an outcome of global improvement in IBS, in IBS patients identified either through clinical practice or through using the ROME criteria. There may be a difference in the severity of patients' IBS between Rahlfs and Mössinger's studies and this study. This is because Ralhfs and Mössinger (Rahlfs and Mossinger 1976; Rahlfs and Mossinger 1979) do not provide a baseline assessment of the severity of IBS, so it cannot be known to what degree the included patients were suffering. However unless there are significant differences between German patients with IBS and British patients with IBS it is likely that the participants in all three trials were fairly similar. In this PhD study IHT, supportive listening and usual care were compared, with IHT and supportive listening being provided as an adjunct to usual care. The homeopathic treatment was individualised homeopathic treatment rather than clinical homeopathy, whereas Rahlfs and Mössinger's studies were assessing clinical homeopathy. The time frame of the studies was also different. The study length in Rahlfs and Mössinger's studies was only 15 days. This is considered to be a relatively short amount of time in terms of homeopathic treatment, which can often take many months (Barry 2006). The time frame for this PhD study was 26 weeks which is considerably longer. Although it is tempting to combine studies in a meta-

analysis, especially if it is likely that a significant result will be yielded, it is important not to combine studies when there is significant clinical heterogeneity, as was the case with these studies. This is because the results from a meta-analysis of the combined studies would not be meaningful due to the large degree of differences between the studies. E.g. they involved different types of homeopathy, were assessed at different time scales (2 weeks compared to 26 weeks) and were potentially comparing people with different levels of disease. Therefore the studies were not considered sufficiently similar for a meta-analysis to be carried out. However a comparison of the results has been made in a Forest plot. The forest plot is displayed in Figure 11-1. To prevent unit of analysis issues that could arise because this study is a three armed trial, the number of participants in the homeopathic treatment arm was divided in half as was the case for the placebo arm in Rahlfs and Mössinger 1976. This is because there are two comparisons involving the homeopathic treatment arm, one comparing homeopathic treatment to usual care and the other comparing homeopathic treatment to supportive listening. In Figure 11-1, Peckham et al 2012a is the comparison of IHT to supportive listening and Peckham et al 2012b is the comparison of IHT with usual care.

The standardised mean was calculated because although all three studies used the same outcome, different scales were used in each of the studies. It can be seen that of the three studies only Rahlfs 1979 showed a statistically significant effect of homeopathic treatment.

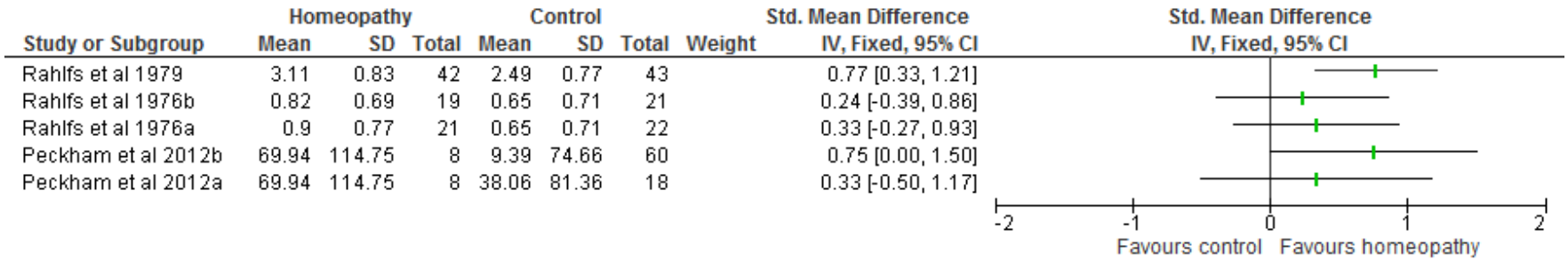

Figure 11-1: Forest plot of three studies

From the Forest plot it can be seen that the current evidence is inconclusive as to whether or not homeopathic treatment may provide a benefit in IBS. When the standardised mean difference (between IHT and usual care) is calculated for the RCT reported in this thesis, no difference is found between IHT and usual care; this is in contrast to the results from the t-test comparing IHT and usual care, yet agrees with the results found in the ANCOVA. This illustrates how different statistical tests can give different results for the same data.

In light of the findings of this systematic review, it is recommended that further studies are carried out to assess the effectiveness of homeopathy, both of IHT and clinical homeopathy. The choice of control for clinical homeopathy is less challenging than for IHT. In the case of clinical homeopathy when a pre-specified remedy, thought to have an affinity with the condition under investigation is to be assessed, a placebo medication provides an appropriate choice of control. However the situation differs for the evaluation of IHT, where the decision as to what is an appropriate control is challenging because of the interconnected nature of the homeopathic remedy and the homeopathic consultation, meaning that it is difficult to separate the two as discussed in Chapter 4. Furthermore the traditional parallel group RCT, where one arm gets a homeopathic consultation plus homeopathic remedy and the other gets a homeopathic consultation plus a placebo remedy, fails to take into account any effectiveness specific to the homeopathic consultation such as the remedy matching process.

11.5 Qualitative study

This section will focus on the qualitative study, beginning with a discussion on recruitment to the qualitative study, before discussing the different typologies and the participants' views on the homeopathic remedy. Finally the views of the homeopaths and counsellor are used to explore how different therapists could have had different impacts on outcomes. This is the first study that explores patients' perceptions of IHT for IBS and compares them with patients' perceptions of supportive listening for IBS.

11.5.1 Impact of recruitment on the results

Due to under recruitment in the RCT it was not possible to use a sampling frame to purposively select participants for the qualitative study, as there

were insufficient numbers. Therefore everyone who had received at least two treatment sessions was invited to attend an interview.

Of those participants who met the eligibility criteria for the interviews, 41.7% of those eligible from the IHT arm and 33% of those eligible from the supportive listening arm consented to be interviewed. This led to five people from the IHT arm and two people from the supportive listening arm being interviewed. Three people from the supportive listening arm had consented to be interviewed, however one of these people was subsequently too ill to be interviewed. From the analysis of those interviewed it was possible to identify four different typologies within those interviewed. However due to the relatively low numbers of people interviewed, especially in the supportive listening arm, it may be that these are not an exhaustive list and had more people been interviewed additional typologies would have been identified. The lack of people interviewed from the supportive listening arm highlights a potential problem for qualitative studies nested within RCTs, in that if the RCT under recruits there is a potential for insufficient eligible participants for the qualitative study. Therefore when carrying out a nested qualitative study it would be useful to estimate the minimum number of participants required in the quantitative study to give an adequate number of participants in the qualitative study.

11.5.2 Patients perceptions of treatment

Overall participants in this study had not used IHT in the past. Only Sheila said that she had previously used a homeopathic remedy, which she had bought over the counter. Thus the participants had little prior knowledge of homeopathy. Apart from Paula (supportive listening, typology two) all participants experienced a benefit that they attributed to the treatment they had received. Paula experienced a benefit but she did not feel she could directly attribute it to the treatment she had received. She could see how the treatment could have helped, but she was reluctant to say that it had definitely helped, as it could have been due to something else. Despite this all participants, including Paula, saw some value in the treatment they received and all participants said that if they were offered the treatment in the future they would take up the offer. This included those who had worsened in terms of their IBS-SSS.

The findings from this study build on previous qualitative research into the homeopathic consultation. By providing information on participants'

perceptions of the whole intervention of IHT, this study presents a broader view of what it is about IHT that patients believe to be of benefit, or not. The homeopathic consultation has in the past been compared to counselling and psychotherapeutic consultations (Chanda and Furnham 2008). Whilst previous studies have identified ways in which the homeopathic consultation differs from counselling and psychotherapeutic consultations (Eyles *et al.* 2010), this is the first study that has directly compared IHT with a counselling type consultation. A difference identified by Eyles was the in-depth enquiry into bodily complaints experienced in the homeopathic consultation. Whilst this is undoubtedly an essential element in IHT (Thompson 2006), none of the patients interviewed in this study spoke of this aspect of the consultation. This may have been because the questions were designed to elicit information on what the patient perceived to have been of benefit and patients did not have a specific viewpoint on the in-depth enquiry into bodily complaints. A difference identified in this PhD study between the homeopathic consultation and supportive listening was the depth to which some of those in the IHT arm explored the mind-body connection. Whilst those in the supportive listening arm were aware of this connection, they did not take it a step further by trying to understand what it was about them and their personalities that led to them getting ill. This is described in more detail in Chapter 10 where the experiences of Sam and Elizabeth (who received IHT) are compared with Mike's (who received supportive listening). Thus, it appears that in some way the homeopathic consultation facilitates the ability for self-exploration through development of the concept of a mind-body connection. These concepts have previously been identified as important to the homeopathic consultation (Thompson and Weiss 2006; Eyles *et al.* 2010; Brien, Leydon and Lewith In press) but as yet no connection has been made between the two.

11.5.3 Participants views on the homeopathic remedy

Through interviewing the participants an insight was gained into what they thought about the homeopathic remedy and whether they believed that the homeopathic remedy would help them. However, whether or not the homeopathic remedy itself led to any physical effects cannot be discerned in this study, and nor was the study designed to assess such results. However the study was designed to explore participants' beliefs about the homeopathic remedy and the role participants believed it played in any improvements observed.

In terms of what people thought about the homeopathic remedy, no one who received IHT thought that the remedy had had no effect. They believed either: that it was the remedy and the consultation that led to a benefit, or that it was the remedy alone. This provides an insight into what people in this study believe about IHT, and the faith people had in the remedy. It may be that had a larger sample been available there would have been some people who believed that the remedy did nothing, and that any improvement was due to the consultation alone. It may also be that some of those who did not consent to being interviewed believed that the remedy did nothing. However the results from this study indicate that people believed that the remedy helped them because they perceived it to have produced changes in their symptoms. Possible mechanisms by which this could have occurred are unknown. However if Moerman (Moerman 2006) is correct in his belief that it is the meanings people hold that lead to improvements, then it is likely that the remedy will lead to an improvement regardless of whether there is anything intrinsically active about the remedy in the way that antibiotics are active. This leads to interesting questions about the potential use of a placebo tablet in the supportive listening arm and the fact that the research ethics committee's views on placebo and how it should be described prevented its use. It also highlights the importance of further research into the mechanisms by which placebos may act.

11.5.4 Importance of who delivered the treatment

Interviews with the therapists gave some insights into both supportive listening and IHT, one of which was the importance of who it was that delivered the treatment and the differences between different people delivering treatment. It has been suggested in psychotherapy that therapist variability far outweighs specific factors of a treatment in terms of treatment effects (Messer and Wampold 2002). In this study Angela, one of the counsellors who provided the supportive listening, thought that having a trained counsellor delivering supportive listening was very different to having a research assistant trained in basic counselling skills delivering supportive listening. This was because Angela believed that being a counsellor affects the whole way a person conducts themselves in respect to patients.

"A research assistant, I don't know I'm making an assumption here so I might be wrong, will not have a clear code of ethics. They may be gifted one that they have got to work in but they won't have the code of ethics which they have to embrace and actually live by." Angela (counsellor)

She thought that this code of ethics would create a different understanding between counsellors providing supportive listening and a research assistant providing supportive listening, because being a counsellor affects the entire way she interacts with patients. Whether or not there is genuinely a difference between a research assistant and a counsellor delivering supportive listening is not known. However the counsellor believed that the understanding between her and the patient led to there being no barriers between her and the patient. This was because the patient knew that they would have absolute confidentiality and that their safety was paramount to her. Mike's experience of his initial meeting with the counsellor demonstrates this lack of barriers.

"It felt like as soon as I met her and sat down took coats off started talking it were, I felt erm safe with her if you know what I mean. I felt confidence with her I felt like I could talk, straight away like I say there were no hurdles no hurdles to start with no physical barriers or ought like that straight away it were good." Mike (patient, supportive listening)

This in part explains why the counsellors had a problem with the wording of the credibility questionnaire because they felt the wording of one of the questions would be detrimental to the patients. Angela felt that being a counsellor was a whole way of being and that counsellors had a set of guidelines by which they lived. To provide the best possible care for the patients whilst adhering to the trials protocol, Angela said that she had stretched the bounds of supportive listening as far as she could. This meant that the supportive listening in this trial was a "boosted up" version of supportive listening and would have been different to a trial where a research assistant with limited training in counselling skills had provide the supportive listening. Thus the interview with the counsellor gave an insight in to the fact that the person delivering the listening can have a significant impact on the treatment. This admission by the counsellor was an interesting admission about the fidelity of the supportive listening intervention. If in fact the counsellors had provided counselling rather than supportive listening, then they could have potentially increased the effect size of supportive listening, resulting in an attenuation of the difference in the effect size between the homoeopathic treatment group in the supportive listening group. This could potentially be a reason why no difference was found between the IHT arm and the supportive listening arm.

The importance of who it is that delivers the treatment was also noted in the IHT arm. On interviewing the homeopaths it became apparent that they used very different styles of practice. One of them would give just one remedy to the patients, whereas the other would give a constitutional remedy to help with their IBS and overall health, and an acute remedy to take during flare ups of IBS. It is likely that these different approaches would impact on the patients differently and that for some people having something to take during an acute episode would be very reassuring. Going back to Moerman's work on meaning (Moerman 2002), it is likely that being given something to take during an acute episode would have meaning for some patients and it is possible that that meaning would translate into a benefit, regardless of whether the remedy had any physical effects on the body.

Including interviews with the practitioners allowed a greater understanding of the therapies as they were delivered, and provided a means of realising the differences between different people delivering the same therapy. In addition the interviews provided a greater understanding of how homeopaths treat people suffering with IBS in the UK. Although homeopaths have presented case studies (Chimthanawala 2004) and written discussion pieces (Gamble 2008) on how they treat IBS, this is the first study that has explored how homeopaths treat IBS patients, not conducted by the homeopath delivering the treatment.

11.5.5 Limitations of the qualitative study

It is possible that this study may not have identified the full range of typologies that exist within the population studied. This is down to two factors: the relatively low numbers of people interviewed, and the fact that the people who agreed to be interviewed may not encompass the full range of possible views. Everyone who agreed to be interviewed perceived, that in some way, the treatment had been helpful and it is unlikely that this constituted the full range of viewpoints. However the four typologies identified allow a broad understanding of how participants perceived the treatment they received.

It is also possible that the methods used to reveal the themes and concerns of the participants in this study may not have captured all the themes and concerns. It is possible when conducting research that a different researcher may come to different conclusions. In this study methods were employed to reduce the chance of this occurring, and to ensure that the study was

conducted in a rigorous manner. These involved sharing transcripts and codes with a supervisor and discussing themes, patient journeys and typologies with supervisors. Full details of these are given in Chapter 10. The purpose of these were, as far as possible, to ensure that a different researcher was likely to come to similar not contradictory conclusions.

11.6 Synthesising the qualitative and quantitative results

11.6.1 The advantages of comparing the qualitative and quantitative results

To fully explore the results of this study, the results of the RCT and the qualitative study were compared. In order to facilitate a greater understanding, it is important when comparing qualitative and quantitative results to explore areas where there is contradiction between the results (O'Cathain, Murphy and Nicholl 2010). In this PhD study when comparing the qualitative and quantitative results it was noticed that for one person (Elizabeth) there was a discrepancy between what she said in the interview and what she reported in the questionnaire. When interviewed Elizabeth said she had had a significant benefit from treatment, however her questionnaire results did not reflect this. On further exploration it was discovered that the failure to see an improvement in the questionnaire data could be linked to a significant event that caused her to become depressed, consequently when she filled out the questionnaire she was depressed and reported how she was feeling at that point in time. In the qualitative interview she discusses how the treatment she received led to an improvement in her health. This case illustrates how linking the qualitative and quantitative data can give a deeper insight into the individual patient. In the case of Elizabeth if only the quantitative data had been studied the conclusion would have been that this person had not improved. Just looking at the qualitative data would have led to the conclusion that this person was significantly helped. However by comparing the two together and exploring the observed discrepancy a deeper understanding of not only Elizabeth’s journey but also the nature of IBS and triggers leading to a deterioration of symptoms could be discovered. This also highlights the fact that questionnaires are completed at a point in time and therefore the answers are affected by how that person feels at that point, which may not necessarily reflect how any treatment they received has impacted on them. The process of randomisation means that

theoretically this effect should be evenly distributed throughout all arms of the trial.

Furthermore Elizabeth's experience demonstrates the effect a significant event can have on IBS and the interaction between stress and IBS. Although this interaction may have been reported by patients, it would not have been observed as clearly had solely a qualitative or solely a quantitative study been carried out.

11.6.2 Different views of treatment

Through comparing the results of the qualitative and quantitative studies, it can be seen that IHT was viewed differently to supportive listening. The typologies that people were in, in the two arms were different. Those in the IHT arm were in either, typology three: it was the remedy, or typology four: it was the remedy and the consultation, whilst those in supportive listening were in either, typology one: listening helps, or typology two: something's worked but I don't know what. It should be borne in mind, however, that a small number of people were interviewed and the results may be slightly different had more people been interviewed. However the results from the RCT indicated that people found IHT more acceptable as already explained, therefore combining these two findings indicates that IHT is indeed viewed differently to supportive listening. In part it is believed to be the remedy accounts for some of these differences in views, people viewed the homeopathic remedy as an important part of the treatment, no one felt it had no action and even those who valued the consultation aspect of IHT believed the remedy to be important.

The homeopathic remedy is not the only way in which IHT differs from supportive listening, the way the talking is conducted is different in IHT. As described in Chapter 10, Sam and Elizabeth found the homeopathic consultation challenging at first, and it wasn't what they had been expecting. No one in the supportive listening arm mentioned this. It may be that those allocated to the supportive listening arm who didn't want to talk about themselves declined the offer of supportive listening. Yet people who didn't want to talk about themselves who were offered IHT, may not have been aware of what IHT involved, and therefore may not have turned down the offer. Therefore there may have been more people in the IHT arm that weren't comfortable talking about themselves than were in the supportive listening arm. The supportive listening aimed to allow the patient to talk with

minimal guidance and questioning. Whereas in IHT to allow the prescription of an appropriate remedy a detailed understanding of the patient is required (Vithoulkas 1998), thus it is also likely that supportive listening was less challenging than IHT.

In summary, the talking in the IHT arm was slightly different to the talking in the supportive listening arm. In the IHT arm the talking facilitated a greater understanding of what caused the patient's IBS, rather than just letting out their concerns, as was the case in the supportive listening arm. However in order to really understand the differences in the styles of the consultations, tapes of both the IHT and supportive listening arms would have to be listening to and analysed.

11.6.3 Supportive listening as an attention control for IHT

One of the aims of this study was to design a suitable control for IHT, in terms of controlling for the non-specific effects of spending time with an empathetic practitioner. Supportive listening was chosen as the control treatment, however in light of the results the question as to whether or not supportive listening is an appropriate control for IHT needs to be explored.

As explained in Chapter 5, the concept of structural equivalence is important when considering an attention control (Baskin *et al.* 2003). In this study supportive listening was able to provide structural equivalence in terms of time spent with a practitioner, however fewer people in the supportive listening arm attended all five sessions that in the IHT arm. If the fact that fewer people attended all the sessions was due to a lack of credibility in the supportive listening then this could lead to the conclusion that supportive listening is not a suitable control. Unfortunately due to issues with the return of the credibility questionnaire it is only possible to estimate whether or not supportive listening was credible based on the questionnaires that were returned. The issue with this is that those who didn't return the questionnaire may not have done so because they didn't believe supportive listening to be credible. Despite this, comparing the results indicates that IHT and supportive listening were similar in terms of credibility. It could therefore be that participants did not complete the five sessions, not because the treatment lacked credibility but because they were not gaining the benefits they desired from the treatment.

In terms of the empathy of the practitioners, this was similar in both arms, indicating that supportive listening is similar to IHT in terms of consultational

empathy. This was important as it has been suggested that therapists can play more of a role in improvement than the specific effects of the therapy itself. (Messer and Wampold 2002). However the fact that fewer people took up the offer of supportive listening cannot be ignored. It may be that people had less faith in supportive listening than IHT, or that they did not want what they perceived to be some sort of cognitive behavioural therapy, or they simply didn't understand what supportive listening was. One person wrote in the free text box in their initial questionnaire that they were happy to try IHT but did not want cognitive behavioural therapy, it is possible that they were not the only person that felt this way. Apart from Sheila in the IHT arm, none of the other participants had any experience of homeopathy or knew much about it, however this did not appear to deter people from taking up the offer of IHT.

Assessing the results of this study, further work needs to be carried out into exploring the appropriateness of supportive listening as a control for IHT. The appropriateness of supportive listening will in part be determined by the condition being studied. For some conditions supportive listening may not be perceived as very credible. In terms of IBS further work needs to be carried out to assess how credible supportive listening is as a control for IHT for IBS. This would require exploring IBS patients views of supportive listening. A possible means of doing this would be by providing IBS patients with information about supportive listening and then asking them questions about whether they thought it would help with their IBS and would it be a treatment they would be likely to accept if they were offered it.

11.7 Strengths and limitations

The strength of this study is that it assesses IHT as it is delivered in practice without seeking to reduce IHT into component parts. In IHT the remedy and the consultation are deeply connected (Milgrom and Chatfield 2011). Therefore trying to dissemble IHT into its constituent parts may not lead to a full picture as to whether or not IHT is effective in the condition to be studied. This study has therefore compared IHT to an attention control in an attempt to control for spending time with an empathetic practitioner. Including a qualitative element to the study has given an added depth to the data, therefore this study gives a fuller view of IHT and supportive listening for IBS than would have been the case had solely a RCT been conducted.

Furthermore the qualitative element allowed an exploration of how the treatment worked rather than solely whether it worked or not.

One of the limitations of this study is that it was underpowered and it has not been able to determine whether or not IHT is better than supportive listening in terms of change in IBS-SSS. Despite this it has shown IHT to be more acceptable to IBS patients than supportive listening. The under-powering of the RCT led to fewer eligible participants for the qualitative study and because of this it may be that there were other viewpoints that were not represented by those who participated in the qualitative interviews. Furthermore the people who agreed to take part in the qualitative study may not be representative of the population who received IHT or supportive listening. This is because people that didn't find a benefit with treatment may not have consented to be interviewed. Everybody who was interviewed found some benefit from the treatment, however it is unlikely that everyone who received a treatment benefited.

11.8 Contribution to the knowledge

The systematic review conducted in this thesis makes a modest contribution to the overall knowledge base on IHT for IBS, in that this is the first time the evidence for the effectiveness of IHT for IBS has been systematically reviewed. Although it was not possible to give a conclusive recommendation as to whether or not homeopathy is effective in the treatment of IBS, it was able to conclude that further trials were warranted.

The RCT has made a contribution to the knowledge regarding the design of trials to explore the effectiveness of IHT. It has shown that whilst it is possible to use a design that compares IHT to an attention control treatment, care has to be taken to ensure that the attention control treatment is credible for the condition being treated.

This study has made a significant contribution to the knowledge regarding what, if anything NHS patients receiving IHT perceive to have been helpful about their treatment. Although a prior study has explored patients views of what was helpful about the homeopathic consultation (Brien, Leydon and Lewith In press), this is the first study to explore patients' views on the whole intervention of IHT rather than solely the consultation aspect. All patients who were interviewed as part of this PhD study perceived the homeopathic remedy to have been of benefit, whilst some patients perceived an additional

benefit from the consultation. This provides a greater understanding of the perception by patients' of IHT. The study has also provided an insight into the fact that the way the talking is conducted and its effects are different in a homeopathic consultation to a supportive listening consultation.

11.9 Implications for practice and policy

The results from the systematic review indicate that IHT may be superior to placebo, however the results from the meta-analysis should be treated with caution due to the low quality of reporting in the trials included in the meta-analysis. The low quality of reporting means that the risk of bias of these studies could not be adequately assessed, however it is believed to be likely that a selection bias may exist. This could have led to an increase in the treatment effect for IHT. In addition to this the studies by Ralhfs and Mössinger (Rahlfs and Mossinger 1976; Rahlfs and Mossinger 1979) were both assessing clinical homeopathy, whilst the trial in this PhD was assessing IHT. These two forms of homeopathic treatment are very different and it may be that one of these forms of homeopathic treatment is more effective than the other. Therefore concluding that IHT is effective based on the results of a meta-analysis of studies of clinical homeopathy may be misleading.

The results from the RCT comparing IHT to usual care and IHT to supportive listening do not show a conclusive benefit of IHT, however the trial was underpowered therefore caution should be exerted when interpreting these results. This is because there is a chance of concluding there is no benefit when really there is a benefit. This means that whilst the results do not clearly provide evidence for the removal of homeopathy from the NHS they also do not mean that homeopathy should definitely be available on the NHS in the treatment of IBS. Furthermore the results from the qualitative study indicated that patients perceived a benefit from receiving IHT. Given the results of this RCT, if there was already a treatment available that clearly benefited IBS patients, then the continued exploration of IHT for IBS may be unwarranted. However as this is not the case it would be beneficial to further explore any potential benefits of IHT for IBS.

11.10 Future work

It is recommended that in the future work is carried out to further assess the suitability of supportive listening as a control treatment for IHT. If supportive listening is found to be suitable, it would be useful to carry out a fully powered RCT comparing usual care, IHT and supportive listening, to further understand the differences between homeopathic treatment and spending time with an empathic practitioner. However unless there was an already established cohort from which participants could be recruited, it would be preferable to carry out a parallel RCT. This is due to the logistics and expense of the BIBSC as described in Section 11.2.3.

In terms of the cmRCT design, it would be of benefit to explore the consent process used in the cmRCT design, with respect to what people understood about what they were consenting to. It is believed that some people did not fully understand this process. This was because the number of people who filled out the questionnaire but failed to consent to the use of the data, yet consented to be contacted again, leads to the suspicion that some people were uncertain about what they were consenting to. Knowledge of what people did and didn't understand about the consent process would allow for any adjustments to be made to the explanation of the consent process, and the consent process itself, that would minimise confusion.

Furthermore in addition to repeating the RCT it would be useful also to conduct qualitative interviews with RCT participants, as was the case with this PhD study. Interviewing a greater number of people could lead to further insights into the four typologies already identified and the discovery of additional typologies. In addition it would be of value to determine whether anyone receiving IHT would fit into typology one: listening helps rather than solely the two typologies that believed the remedy to be of benefit i.e. typology three: it was the remedy or typology four: it was the remedy and the consultation.

Furthermore, it would be of benefit to the practice of IHT and its potential provision, to explore the notion of responders and non-responders and determine whether there are in fact responders and non-responders to IHT, and if so what are the particular characteristics that lead to a person being a responder.

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Appendices

Appendix 1

Searches for specific and non-specific effects of homeopathic treatment

Search 1 – 14th June 2012

A search was carried out in Web of Science using the terms:

("specific effect*" or "context effect*") and homeopath* (28)

OR

"non specific effect" and homeopath* (6)

The number in brackets indicates the number of studies identified.

Search 2 – 14th June 2012

Database: AMED (Allied and Complementary Medicine) 1985 to June 13 2012.

The search was modified for Embase Classic and Embase (1947 to June 13 2012) and Ovid MEDLINE(R) (1950 to June Week 1 2012).

Search Strategy

Search number	Search term	Number of hits identified		
		AMED	Embase Classic + Embase	MEDLINE
1	"specific effect*" .mp. [mp=abstract, heading words, title]	188	16 882	4 277
2	"context effect*" .mp. [mp=abstract, heading words, title]	29	914	175
3	Exp homeopathy/	11 340	7 764	3 937
4	1 OR 2	217	17 793	4 464
5	3 AND 4 (14) (27)	14	27	5

Appendix 2

Searches for trials of homeopathic treatment for irritable bowel syndome

Search 1 – 14th June 2012

A search was carried out in Web of Science using the terms:

“irritable bowel syndrome” OR “irritable bowel disease” OR “irritable colon”

AND

“homeopath*” OR “homoeopath*” (16)

The number in brackets indicates the number of studies identified.

Search 2 – 14th June 2012

Database: AMED (Allied and Complementary Medicine) (1985 to June 2012)

The search was modified for Embase Classic + Embase (1947 to 2012 June 14) and Ovid MEDLINE (1946 to June week 3 2012)

Search Strategy

Search number	Search term	Number of hits identified		
		AMED	Embase Classic + Embase	MEDLINE
1	irritable bowel syndrome” .mp. [mp=abstract, heading words, title]	209	10 051	6 996
2	irritable bowel disease” .mp. [mp=abstract, heading words, title]	1	135	6 996
3	“irritable colon” .mp. [mp=abstract, heading words, title]	1	13 720	391
4	Exp irritable bowel syndrome/	790	13 587	3 378
5	1 OR 2 OR 3 OR 4	210	15 106	7 364
6	Exp homeopathy/	11 340	7 778	3 889
7	5 AND 6	15	50	6

Appendix 3

Searches for attention controls in IBS trials

Search 1 - 21st June 2012

Database: Ovid MEDLINE(R) (1950 to June Week 2 2012). The search was modified for PsycINFO (1806 to June Week 2 2012) and Embase Classic + Embase (1947 to June 20 2012).

Search Strategy

Search number	Search term	Number of hits identified		
		MEDLINE	PsycINFO	Embase Classic + Embase
1	exp Irritable Bowel Syndrome/	3 365	681	13 561
2	"attention* placebo".mp. [mp=title, abstract, heading word, table of contents, key concepts]	113	252	169
3	"attention* control".mp. [mp=title, abstract, heading word, table of contents, key concepts]	1 350	1 939	1 776
4	"supportive listening".mp. [mp=title, abstract, heading word, table of contents, key concepts]	22	27	28
5	“supportive counselling".mp. [mp=title, abstract, heading word, table of contents, key concepts]	58	48	86
6	"supportive therapy".mp. [mp=title, abstract, heading word, table of contents, key concepts]	2 319	556	3 697
7	2 OR 3 OR 4 OR 5 OR 6	3 856	2 825	5 746
	8 1 AND 7	10	8	23

Search 2 -21st June 2012

Searches were carried out in Web of Science using the terms:

1. “attention* placebo” AND “irritable bowel syndrome” OR “attention* control” AND “irritable bowel syndrome” (6)
2. (“supportive listening*” AND “ irritable bowel syndrome”) OR (“supportive therapy” AND “ irritable bowel syndrome”) OR (“supportive counselling*” AND “ irritable bowel syndrome”) (18)
3. “relaxation” AND “ irritable bowel syndrome” (311)

Numbers in brackets indicate the number of studies identified in each of the searches.

Appendix 4

Provenance statement from wider trial

JR, CW, KK, CS originally conceived the idea for a HIBS RCT to address the primary research question, and obtained the initial seed funding from Barnsley Hospital Small Grant Fund. CS, JR, EG & CR wrote the original protocol. EP conceived the idea for the secondary research question. CR applied the ‘cohort multiple RCT’ design to the original and secondary research question. KT provided guidance throughout. CR & EP wrote the protocol.

KT and EP are supported and funded by the University of Leeds. CR was supported by the University of Leeds and is now supported by the University of Sheffield.

For any peer reviewed publications that derive from this study the following authors will be eligible for authorship: JR, CW, KK, ES, CS, KT, EP, CR, EG.

Appendix 5

Searches of IBS trials that had used an attention control

Search 1 – 19th June 2010

Database: AMED (Allied and Complementary Medicine) 1985 to June 2010.

The search was modified for Embase (1996 to 2010 Week 22) and Ovid Medline (1996 to May Week 4 2010)

Search Strategy

Search number	Search term	Number of hits identified		
		AMED	Embase	Ovid Medline
1	"specific effect*" .mp. [mp=abstract, heading words, title]	52	2 679	2 193
2	"context effect*" .mp. [mp=abstract, heading words, title]	0	135	88
3	Exp irritable bowel syndrome/	72	8 910	2 790
4	Exp colonic diseases/	0	184 295	90 102
5	Exp colonic diseases, functional/	0	8 910	4 655
6	"irritable bowel*" .mp. [mp=abstract, heading words, title]	214	7 316	5 128
7	"irritable colon" .mp. [mp=abstract, heading words, title]	1	8 924	47
8	"spastic colon" .mp. [mp=abstract, heading words, title]	4	18	9
9	"functional bowel disease*" .mp. [mp=abstract, heading words, title]	0	113	58
10	"functional colonic disease*" .mp. [mp=abstract, heading words, title]	0	3	0
11	1 OR 2	52	2 814	2 281
12	3 OR 4 OR 5OR 6OR 7 OR 8 OR 9 OR 10	217	185 169	91 226
13	1 AND 3	0	42	23

Appendix 6

Invitation to the Cohort

UNIVERSITY OF LEEDS

GP Address

Date

Barnsley Irritable Bowel Syndrome Cohort Study

Dear XXXX

I warmly invite you to take part in the Barnsley Irritable Bowel Syndrome Cohort Study.This study will provide valuable information to help the NHS make decisions about what type of treatments and services to provide to people with IBS in the future. This study aims to recruit 600 patients from our GP practice and others within Barnsley PCT to obtain this information.

Please read the enclosed Information Sheet carefully. This tells you more about the study and what happens if you agree to take part. If you want to ask any questions, please ask Dr Kapil Kapur at C/o Gastroenterology Dept, Barnsley Hospital NHS Foundation Trust, Gawber Road, Barnsley,S75 2EP or Emily Peckham School of Healthcare, Baines Wing, University of Leeds, LS2 9JT, 0113 3433201, Email: hcejp@leeds.ac.uk.

I want to assure you that the information you provide the researchers with will be kept *strictly confidential*. Your name will not be mentioned in any reports or given to anyone outside the research team.

If you are happy to take part in the study, please now complete the enclosed Questionnaire and sign the Consent Form on the back and send it back to the researchers.

Thank you for sparing the time to read through this, if you choose, for taking part in this important research study.

Yours Sincerely

Dr XXXX

Practice Name

Patient Information Sheet for Cohort Study

Barnsley Irritable Bowel Syndrome Cohort Study

We would like you to take part in a research study. Before you decide, you need to understand why this study is being done and what it will involve for you.
Please take time to read the following information carefully.
Talk to others about the study if you wish.
Ask us if there is anything that is not clear or if you would like more information.
Take time to decide whether or not you wish to take part.
Thank you for taking the time to read this.

What is the purpose of the study?

The purpose of this study is to follow approximately 600 adults in Barnsley who have visited their GP or consultant with IBS type symptoms and to collect information about their health, general well being and any treatments they are receiving. This study will provide valuable up to date information on IBS.

About 1 in 20 people who have chosen to participate in this study will be randomly selected to be offered a treatment. We currently want to test the effectiveness of the following two treatments:
1. Homeopathic treatment
2. Supportive listening

Inclusion in the study **does not necessarily mean** that you will be offered one of the above treatments. If you are randomly selected to be offered one of the treatments you will be sent a separate letter and an information sheet with further details describing the treatment offered. It is entirely up to you whether or not you choose to take up the offer and it will not affect any of your future care or treatment within the NHS.

Why have I been chosen?

You have been chosen because you have had either a diagnosis of IBS or are taking medication commonly prescribed for those suffering from IBS.

Do I have to take part?

No participation is entirely voluntary. Not taking part will not affect any of your future care or treatment within the NHS. No one will know that you have

not agreed to take part in the study. Even if you take part now, you can decide not to take any further part in the study by not completing any further questionnaires that we send you. You do not have to give any reasons.

What will happen to me if I take part?

If you agree to take part you please complete the enclosed Questionnaire and return it to the researchers at the University of Leeds. This information will be very helpful to the researchers and the NHS.

What do I have to do?

Complete and return Questionnaire number 1 in the pre paid envelope provided.

- Continue your life as normal, continuing to take your medication as before.

What are the possible benefits of taking part?

There are no benefits to you personally, however if you take part you will be **helping us to advance** understanding of IBS. The information we gather from this study may help us to treat patients with IBS in the future.

What are the possible disadvantages of taking part?

You will have to make time to complete the questionnaires.

What if there is a problem?

Any complaint about the way you have been dealt with during the study will be addressed. If you have a concern about any aspect of this study, you should ask to speak with the Patient Advice and Liaison Service (PALS) at Barnsley Hospital. The address is below:
Patient Advice and Liaison Service, Main Reception, Barnsley Hospital NHS Foundation Trust, Gawber Road, Barnsley, S75 2EP

Tel: 01226 730000 Ext: 2430

Will my taking part in this study be kept confidential?

All information that you give us will be kept strictly confidential. Your name will not be mentioned in any reports. Only members of the research team will know that you have agreed to take part in the study.

As we will be sending you further questionnaires we need your name and contact details. These personal details will be stored in locked filing cabinets and all electronic copies will be stored on a secure server accessed by password – protected computers at the University of Leeds.

We will ask your permission to write to your GP and inform them that you are involved in the study and this is only for their information.

What will happen to the results of the study?

The data that you provide will be anonymised and may be used in the future to compare treatments for IBS. The results of the study will be presented at conferences and submitted to a scientific journal for publication. We expect this to happen within 6 months of the end of the study. We will also write a short report for all participants and this will be sent to you and your GP. You will not be identified in any reports or publications.

Who is organising and funding the study?

Dr Kapil Kapur who is a Consultant Gastroenterologist at Barnsley Hospital is leading the study. The Barnsley Health and Social Care R&D Alliance small projects fund and Friends of Barnsley Hospital are funding the study.

Who has reviewed the study?

The study has been reviewed by Leeds East Research Ethics Committee and by the Consumers in Research Advisory Group at Barnsley Hospital.

Contact for further information

Dr Kapil Kapur, C/o Gastroenterology Dept, Barnsley Hospital NHS Foundation Trust, Gawber Road, Barnsley, S75 2EP or Emily Peckham, School of Healthcare, Baines Wing, University of Leeds, LS2 0113 3433201, Email: hcejp@leeds.ac.uk

Thank you for taking this the time to read this information sheet.

Please keep this copy.

Consent Form

Thank you for your answers. These will be combined with hundreds of others. What we learn will help us understand how we can improve the health of people with irritable bowel syndrome.

We would like to contact you again.
Please tick the box to indicate your consent. ☐

We would like to use the information you provide to look at the benefit of health treatments for IBS.
Please tick the box to indicate your consent. ☐

We would like to look at your health records.
Please tick the box to indicate your consent ☐

Please fill in your **forename**, **surname** and **address** if different to those printed to the left.

Forename (print)

Surname (print)

Address

Postcode

Please fill in your preferred contact details below:

Telephone

Mobile phone*

Email*

*Optional

Signature .....

Thank you for completing the Health Questionnaire. Please put it in the prepaid envelope and post it to the researchers. NO STAMP NEEDED.

If you have any queries or require further information about this study, please contact Emily Peckham, School of Healthcare, University of Leeds, LS2 9JT
Email: hceip@leeds.ac.uk **Tel:** 0113 3433201

UNIVERSITY OF LEEDS

Barnsley Hospital NHS
NHS Foundation Trust

Health Questionnaire 1

Barnsley Irritable Bowel Syndrome Cohort Study

Welcome to the Barnsley Irritable Bowel Syndrome Cohort Study! Please help us by filling in this questionnaire. Your answers will help us understand how we can improve the health of people with IBS.
The questionnaire will take 10-15 minutes to complete. When you have completed the questionnaire, please put it in the envelope and post it to the researchers at the University of Leeds. You do not need a stamp.

About you

Your sex Male ☐ Female ☐

Your date of birth ☐☐ ☐☐ ☐☐☐☐

d d m m y y y y

Which ethnic group do you belong to?

White		Asian or Asian British		Mixed	
British	☐	Indian	☐	White and Black Caribbean	☐
Irish	☐	Pakistani	☐	White and Black African	☐
Other white background	☐	Bangladeshi	☐	White and Asian	☐
		Other Asian background	☐	Other mixed background	☐
Black or Black British		**Chinese or other ethnic group**		**Gypsy / traveler**	
Caribbean	☐	Chinese	☐	Gypsy / traveler	☐
African	☐	Other ethnic group	☐		
Other Black background	☐				

Your Work

Are you currently employed? Yes ☐ No ☐

Your Health

Here are some simple questions about your health in general[1]. By ticking one answer in each group below, please indicate which statements best describe your own health state TODAY

Mobility	Please tick one
I have no problems in walking about	
I have some problems in walking about	
I am confined to bed	
Self-care	**Please tick one**
I have no problems with self-care	
I have some problems washing or dressing myself	
I am unable to wash or dress myself	
Usual Activities	**Please tick one**
I have no problems with performing my usual activities (e.g. work, study, housework, family or leisure activities)	
I have some problems with performing my usual activities	
I am unable to perform my usual activities	
Pain / Discomfort	**Please tick one**
I have no pain or discomfort	
I have moderate pain or discomfort	
I have extreme pain or discomfort	
Anxiety / Depression	**Please tick one**
I am not anxious or depressed	
I am moderately anxious or depressed	
I am extremely anxious or depressed	

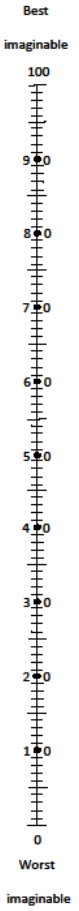
[1] *© 1990 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group*

If there anything else you would like to add, please use the space below.

To help people say how good or bad a health state is, we have drawn a scale[1] (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



[1] *© 1990 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group*

Your Health

During the last 3 MONTHS

How many days have you taken off from paid work as a result of illness? ☐☐ Days

How many days has ill health prevented you from carrying out your:

Leisure activities ☐☐ Days Household tasks ☐☐ Days

Long term conditions

Do you have any long-standing illness, health problem, condition or disability? Yes ☐ No ☐

If yes, please tick all that apply:

Breathing problems e.g. Chronic Bronchitis or emphysema		Psychiatric disorder e.g. schizophrenia or bi-polar	
Cancer		Haemophilia	
Colitis		Heart Disease	
Crohn's disease		High blood pressure	
Depression/ Anxiety		Insomnia	
Diabetes		Osteoarthritis	
Fatigue or Tiredness		Other	

Have you had gastrointestinal surgery in the last 6 months? Yes ☐ No ☐

For women: Are you pregnant or breast feeding? Yes ☐ No ☐

Your medication

Are you currently taking any medication, including medication for Irritable Bowel Syndrome?

Yes ☐ No ☐

Please list all your medication below; including all medication prescribed by your doctor and medication that you buy yourself, such as vitamins & mineral supplements, dietary supplements or diet pills, herbal or homeopathic remedies. Continue on a separate sheet if necessary.

Name & strength of tablet, medicine, ointment, drops, inhaler or injection	Is this prescribed for you? Please tick:		What is this for?
(Example) Co-codamol 8mg/500mg tablets	Yes	No	Joint pain

Your Healthcare

In the last 6 MONTHS, how many times have you visited the following, for any complaint?

Hospital	Times
Accident & Emergency (A&E)	☐☐
Hospital - day case	☐☐
Hospital - outpatients	☐☐
Hospital - in-patients (how many nights)	☐☐

Other health professionals	Times
GP	☐☐
Nurse	☐☐
Physiotherapist	☐☐
Dietitian	☐☐
Midwife	☐☐
Mental health worker	☐☐
Psychotherapist	☐☐

Other Carers	Times
Counsellor	☐☐
Care worker	☐☐
Social worker	☐☐
Health visitor	☐☐
Community health champion	☐☐
Health trainer	☐☐

Alternative therapist	Times
Acupuncturist	☐☐
Chiropractor	☐☐
Herbalist	☐☐
Homeopath	☐☐
Osteopath	☐☐

Other *please describe:*	Times
	☐☐

Your IBS symptoms

Please tick one answer.

1. In the last three months, how often did you have discomfort or pain anywhere in your abdomen? **If answer never, skip the remaining questions**	Please tick one.
Never	
Less than one day a month	
One day a month	
Two to three days a month	
One day a week	
More than one day a week	
Every day	
2. For women: Did this discomfort or pain occur only during your menstrual bleeding and not at other times?	**Please tick one.**
No	
Yes	
Does not apply because I have had the change in life (menopause) or I am a male	

Your Mood

Read each item and tick the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I have lost interest in my appearance:	**Please tick one**
Definitely	
I don't take so much care as I should	
I may not take quite as much care	
I take just as much care as ever	
I feel restless as if I have to be on the move:	**Please tick one**
Very much indeed	
Quite a lot	
Not very much	
Not at all	
I look forward with enjoyment to things:	**Please tick one**
As much as ever I did	
Rather less than I used to	
Definitely less than I used t o	
Hardly at all	
I get sudden feelings of panic:	**Please tick one**
Very often indeed	
Quite often	
Not very often	
Not at all	
I can enjoy a good book or radio or TV programme:	**Please tick one**
Often	
Sometimes	
Not often	
Very seldom	

Other information

Are you participating in any other study of treatments for IBS or any other medical condition?

Yes ☐ No ☐

Have you been in a study of treatments of IBS in the last 3 months?

Yes ☐ No ☐

Your Mood

Read each item and tick the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up'	Please tick one
Most of the time	
A lot of the time	
From time to time, occasionally	
Not at all	
I still enjoy the things I used to enjoy:	**Please tick one**
Definitely as much	
Not quite so much	
Only a little	
Hardly at all	
I get a sort of frightened feeling as if something awful is about to happen:	**Please tick one**
Very definitely and quite badly	
Yes, but not too badly	
A little, but it doesn't worry me	
Not at all	
I can laugh and see the funny side of things:	**Please tick one**
As much as I always could	
Not quite so much now	
Definitely not so much now	
Not at all	
Worrying thoughts go through my mind:	**Please tick one**
A great deal of the time	
A lot of the time	
From time to time but not too often	
Only occasionally	
I feel cheerful:	**Please tick one**
Not at all	
Not often	
Sometimes	
Most of the time	
I can sit at ease and feel relaxed:	**Please tick one**
Definitely	
Usually	
Not often	
Not at all	
I feel as if I am slowed down:	**Please tick one**
Nearly all the time	
Very often	
Sometimes	
Not at all	
I get a sort of frightened feeling like "butterflies" in the stomach:	**Please tick one**
Not at all	
Occasionally	
Quite often	
Very often	

3. Have you had this discomfort or pain 6 months or longer?	Please tick one.
No	
Yes	
4. How often did this discomfort or pain get better or stop after you had a bowel movement?	**Please tick one.**
Never or rarely	
Sometimes	
Often	
Most of the time	
Always	
5. When this discomfort or pain started, did you have more frequent bowel movements?	**Please tick one.**
Never or rarely	
Sometimes	
Often	
Most of the time	
Always	
6. When this discomfort or pain started, did you have less frequent bowel movements?	**Please tick one.**
Never or rarely	
Sometimes	
Often	
Most of the time	
Always	
7. When this discomfort or pain started, were your stools (bowel movements) looser?	**Please tick one.**
Never or rarely	
Sometimes	
Often	
Most of the time	
Always	
8. When this discomfort or pain started, how often did you have harder stools?	**Please tick one.**
Never or rarely	
Sometimes	
Often	
Most of the time	
Always	
9. In the last 3 months, how often did you have hard or lumpy stools?	**Please tick one.**
Never or rarely	
Sometimes	
Often	
Most of the time	
Always	
10. In the last 3 months, how often did you have loose, mushy or watery stools?	**Please tick one.**
Never or rarely	
Sometimes	
Often	
Most of the time	
Always	

Irritable Bowel Syndrome Symptom Severity Scale

It is expected that your symptoms might vary over time, so please try and answer these questions based on how you currently feel (ie over the last 10 days or so).

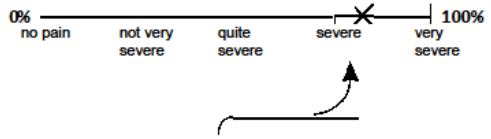
For questions where a number of different responses are a possibility please circle the response appropriate to you.

1. Some questions will require you to write in an appropriate response.

2. Some questions require you to put a cross on a line which enables us to judge the severity of a particular problem.

For example:

How severe was your pain?



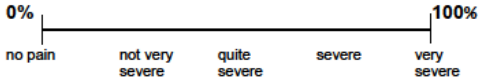
this answer would indicate that pain is approximately 80% severe

Please answer the following questions.

1 a) Do you currently suffer from abdominal (tummy) pain? YES NO

Circle appropriate box

b) If yes, how severe is your abdominal (tummy) pain?



c) Please enter the number of days that you get the pain in every 10 days.

For example if you enter 4 it means that you get pain 4 out of 10 days. If you get pain every day enter 10

Number of days with pain

*2 a) Do you currently suffer from abdominal distension**

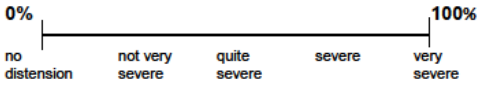
(bloating, swollen or tight tummy)

*(*women, please ignore distension related to your periods)*

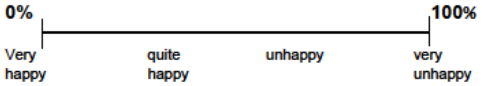
YES NO

Circle appropriate box

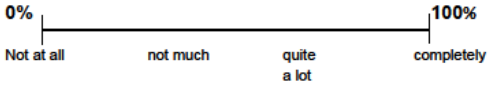
b) If yes, how severe is your abdominal distension/tightness



3 How satisfied are you with your bowel habit?



4 Please indicate with a cross on the line below how much your Irritable Bowel Syndrome is affecting or interfering with your life in general.



Appendix 7

Invitation letter for Homeopathic treatment

Barnsley Hospital NHS
NHS Foundation Trust

UNIVERSITY OF LEEDS

School of Healthcare
Baines Wing
University of Leeds
LS2 9JT

Homeopathic treatment for Irritable Bowel Syndrome.

Dear

We are writing to invite you to take part in a study of homeopathic treatment for Irritable Bowel Syndrome. This study will provide valuable information to help the NHS make decisions about what type of treatments and services to provide to people with IBS in the future.

Please read the enclosed Information Sheet carefully. This tells you more about the study and what happens if you agree to take part. If you want to ask any questions, please ask:

Dr Kapil Kapur C/o Gastroenterology Dept, Barnsley Hospital NHS Foundation Trust, Gawber Road, Barnsley, S75 2EP

Emily Peckham School of Healthcare, University of Leeds, 0113 3433201. Email: hcejp@leeds.ac.uk

We would be grateful if you could give this study some consideration and we will telephone you in the week commencing 14th March 2011 to discuss any questions you may have and, if you do wish to take part, arrange an appointment with a homeopath at Barnsley Hospital.

If you decide that you are happy to take part in the study, please sign the enclosed Consent Form and send it back to the researchers. Thank you for

sparing the time to read through this and, if you choose, for taking part in this important research study.

Yours Sincerely

Kapil Kapur
Barnsley Hospital

Emily Peckham
University of Leeds

Patient information sheet for homeopathic treatment

Barnsley Hospital NHS
NHS Foundation Trust

UNIVERSITY OF LEEDS

Information Sheet

Homeopathic treatment for Irritable Bowel Syndrome.

- We would like you to take part in a research study. Before you decide, you need to understand why this study is being done and what it will involve for you.
- Please take time to read the following information carefully.
- Talk to others about the study if you wish.
- Ask us if there is anything that is not clear or if you would like more information.
- Take time to decide whether or not you wish to take part.

Thank you for taking the time to read this.

What is the purpose of the study?

We are conducting an exploratory study to evaluate whether the addition of homeopathic treatment to usual care improves outcomes for patients with a diagnosis of IBS.

Why have I been chosen?

You have been chosen because you previously agreed to take part in an observational study of patients with irritable bowel syndrome. You have been randomly selected from this observational study to be offered homeopathic treatment.

Do I have to take part?

No, it is up to you whether or not you decide to take part. If you do decide to be included you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision to not be included in the study, will not affect the standard of care that you receive.

What is the drug or procedure that is being tested?

Homeopathic treatment involves a consultation with a homeopath followed by the prescription of a homeopathic remedy. It has been available on the NHS since 1948, however there is no clear proof as to whether or not it works. Whilst some patients report a benefit with homeopathic treatment we don't know whether this is the case for more than a handful of people. In this study we are trying to find out if homeopathic treatment improves IBS symptoms.

What will happen to me if I take part?

If you agree to take part in this research project, you will be given a copy of the signed consent form to keep.

You will be involved in the study for 52 weeks. During this time you will be asked to attend Barnsley Hospital for appointments with a homeopath 5 times.

At the end of your second appointment with a homeopath at Barnsley Hospital you will be given a questionnaire to compete and return in the prepaid envelope provided.

What do I have to do?

If you agree to homeopathic treatment we will ask you to attend five appointments with a homeopath and take the prescribed homeopathic remedy. You will continue to take your medication as before.

What are the side effects of any treatment received when taking part?

We do not expect you to have any adverse reaction to the homeopathy treatment. However, you will be given your homeopaths contact number if you have any questions or concerns.

What are the possible benefits of taking part?

You may find an improvement in your condition, but this cannot be guaranteed. The information we gather from this study will help us to treat patients with IBS in the future.

What are the disadvantages of taking part?

You will have to make time to attend the homeopathy appointments.

What happens when the research study finishes?

At the end of the study if you wish to continue homeopathic treatment you will be given details of how to access homeopathic treatment privately or on the NHS.

What if there is a problem?

Any complaint about the way you have been dealt with during the study will be addressed. If you have a concern about any aspect of this study you should contact the Patient Advice and Liaison Service (PALS) at Barnsley Hospital. The address is below:

Patient Advice and Liaison Service, Main Reception, Barnsley Hospital NHS Foundation Trust
Gawber Road, Barnsley, S75 2EP Tel: 01226 730000 Ext: 2430

Will my taking part in this study be kept confidential?

All information that you give us will be kept strictly confidential. Your name will not be mentioned in any reports. Only members of the research team will know that you have agreed to take part in the study. As we will be sending you further questionnaires we need your name and contact details. These personal details will be stored in locked filing cabinets and all electronic copies will be stored on a secure server accessed by password – protected computers at the University of Leeds.

We will ask your permission to write to your GP and inform them that you are involved in the study and this is only for their information.

What will happen to the results of the study?

The results of the study will be presented at conferences and submitted to a scientific journal for publication. We expect this to happen within 6 months of the end of the study. We will also write a short report for all participants and this will be sent to you and your GP. You will not be identified in any reports or publications.

Who is organising and funding the study?

Dr Kapil Kapur who is a Consultant Gastroenterologist at Barnsley Hospital is leading the study. The Barnsley Health and Social Care R&D Alliance small projects fund are funding the study.

Who has reviewed the study?

The study has been reviewed by Leeds East Research Ethics Committee and by the Consumers in Research Advisory Group at Barnsley Hospital.

Contact for further information

Emily Peckham, Baines Wing, School of Healthcare, University of Leeds,LS2 9JT
Tel: 0113 3433201 **Email**: hcejp@leeds.ac.uk

Thank you for taking this the time to read this information sheet.

Please keep this copy.

Consent form for Homeopathic treatment

Barnsley Hospital NHS
NHS Foundation Trust

UNIVERSITY OF LEEDS

Consent Form

Title of project : Homeopathic treatment for Irritable Bowel Syndrome

Research Team ; Dr K Kapur, Mrs J Raw, Mrs C Walters, Ms Emily Peckham,Dr C Relton, Dr E Said, Dr CM Smith, Miss E Goodwin

1. I confirm that I have read and understand the information sheet dated November 2010. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. In this case my medical care or legal rights will not be affected in any way. ☐
3. I give permission for my GP to be informed of my participation in the study ☐
4. I agree to take part in the above study. ☐

_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Invitation letter for supportive listening

Barnsley Hospital NHS
NHS Foundation Trust

UNIVERSITY OF LEEDS

School of Healthcare
Baines Wing
University of Leeds
LS2 9JT

Supportive listening for Irritable Bowel Syndrome

Dear

We are writing to invite you to take part in a study of supportive listening for Irritable Bowel Syndrome. This study will provide valuable information to help the NHS make decisions about what type of treatments and services to provide to people with IBS in the future.

Please read the enclosed Information Sheet carefully. This tells you more about the study and what happens if you agree to take part. If you want to ask any questions, please ask:

Dr Kapil Kapur C/o Gastroenterology Dept, Barnsley Hospital NHS Foundation Trust, Gawber Road, Barnsley,S75 2EP

Emily Peckham School of Healthcare, University of Leeds, 0113 3433201. Email: hcejp@leeds.ac.uk

We would be grateful if you could give this study some consideration and we will telephone you in the week commencing 14 March 2011 to discuss any questions you may have and, if you do wish to take part arrange an appointment with a counselor at Barnsley Hospital.

If you are happy to take part in the study, please sign the enclosed Consent Form and send it back to the researchers. Thank you for sparing the time to read through this and, if you choose, for taking part in this important research study.

Yours Sincerely

Kapil Kapur — Barnsley Hospital

Emily Peckham — University of Leeds

Patient information sheet for supportive listening

Barnsley Hospital NHS
NHS Foundation Trust

UNIVERSITY OF LEEDS

Information Sheet

Supportive listening for Irritable Bowel Syndrome.

- We would like you to take part in a research study. Before you decide, you need to understand why this study is being done and what it will involve for you.
- Please take time to read the following information carefully.
- Talk to others about the study if you wish.
- Ask us if there is anything that is not clear or if you would like more information.
- Take time to decide whether or not you wish to take part.

Thank you for taking the time to read this.

What is the purpose of the study?

We are conducting a study to evaluate whether supportive listening in addition to your usual care will improve outcomes for patients with IBS.

Why have I been chosen?

You have been chosen because you previously agreed to take part in an observational study of patients with IBS. You have been randomly selected from this observational study to be offered supportive listening.

Do I have to take part?

No, it is up to you whether or not you decide to take part. If you do decide to be included you will be given this information sheet to keep and asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision to not be included in the study, will not affect the standard of care that you receive.

What will happen to me if I take part?

If you agree to take part in this research project, you will be given a copy of the signed consent form to keep.

You will be involved in the study for 52 weeks. During this time you will be asked to attend Barnsley Hospital for appointments with a trained professional 5 times.

At the end of your second appointment with a supportive listener at Barnsley Hospital you will be given a questionnaire to compete and return in the prepaid envelope provided.

A selection of the supportive listening appointments will be recorded on an audiotape. This is to ensure that the therapist is providing supportive listening and not a type of counselling such as cognitive behavioural therapy. An independent person will listen to the audiotape to confirm this. After they have listened to the audiotape it will be destroyed. The tape will be anonymised prior to the independent assessor listening to it and they will have no way of identifying you from the tape.

What do I have to do?

If you agree to supportive listening we will ask you to attend 5 appointments with a trained professional at Barnsley Hospital. You will continue to take your usual medication as before.

What is the drug or procedure that is being tested?

Supportive listening will provide you with the opportunity to discuss your IBS with a trained professional. During the sessions you will be encouraged to talk about your physical symptoms as well as any emotional issues and to discuss how these might be coped with in a better way.

Whilst some people find talking to somebody and being supported helpful we don’t know if this is the case for the majority of people and we are trying to find out if supportive listening helps patients with IBS.

What are the side effects of any treatment received when taking part?

We do not expect you to have any adverse reaction to the treatment. You will be given a contact number if you have any questions or concerns.

What are the possible benefits of taking part?

You may find an improvement in your condition, but this cannot be guaranteed. The information we gather from this study will help us to treat patients with IBS in the future.

What are the disadvantages of taking part?

You will have to make time to attend the supportive listening appointments.

What happens when the research study finishes?

At the end of the study, if you wish to continue supportive listening you will be given details of how to access treatment privately or on the NHS.

What if there is a problem?

Any complaint about the way you have been dealt with during the study will be addressed. If you have a concern about any aspect of this study you should contact the Patient Advice and Liaison Service (PALS) at Barnsley Hospital. The address is:

Patient Advice and Liaison Service, Main Reception, Barnsley Hospital NHS Foundation Trust

Gawber Road, Barnsley, S75 2EP

Tel: 01226 730000 Ext: 2430

Will my taking part in this study be kept confidential?

All information that you give us will be kept strictly confidential. Your name will not be mentioned in any reports. Only members of the research team will know that you have agreed to take part in the study. As we will be sending you further questionnaires we need your name and contact details. These personal details will be stored in locked filing cabinets and all electronic copies will be stored on a secure server accessed by password – protected computers at the University of Leeds.

We will ask your permission to write to your GP and inform them that you are involved in the study and this is only for their information.

What will happen to the results of the study?

The results of the study will be presented at conferences and submitted to a scientific journal for publication. We expect this to happen within 6 months of the end of the study. We will also write a short report for all participants and

this will be sent to you and your GP. You will not be identified in any reports or publications.

Who is organising and funding the study?

Dr Kapil Kapur who is a Consultant Gastroenterologist at Barnsley Hospital is leading the study. The Barnsley Health and Social Care R&D Alliance small projects fund are funding the study.

Who has reviewed the study?

The study has been reviewed by Leeds East Research Ethics Committee and by the Consumers in Research Advisory Group at Barnsley Hospital.

Contact for further information

Emily Peckham, Baines Wing, School of Heathcare,University of Leeds, LS2 9JT
Tel: 0113 3433201, **Email:** hcejp@leeds.ac.uk

Thank you for taking this the time to read this information sheet.

Please keep this copy

Consent for supportive listening

Barnsley Hospital NHS
NHS Foundation Trust

UNIVERSITY OF LEEDS

Consent Form

Title of project : Supportive listening Irritable Bowel Syndrome

Research Team ; Dr K Kapur, Mrs J Raw, Mrs C Walters, Ms Emily Peckham,

Dr C Relton, Dr E Said, Dr CM Smith, Miss E Goodwin

1. I confirm that I have read and understand the information sheet dated November 2010 ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. In this case my medical care or legal rights will not be affected in any way. ☐
3. I give permission for my GP to be informed of my participation in the study ☐
4. I give permission for my supportive sessions to be recorded on an audiotape ☐
5. I agree to take part in the above study. ☐

_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Appendix 8

EuroQol Agreement

Dear Ms/Mr. Peckham,

Thank you for registering your research at the EuroQol Group's website.

As the study you registered at the EuroQol website involves low patient numbers (200) and is not funded by a pharmaceutical company/medical device manufacturer, or any other profit-making stakeholders, you may use the EQ-5D instrument free of charge. If this is not the case, or the situation changes, please inform us as the EuroQol Group Foundation has a specific policy for large academic studies and/or studies funded by profit making bodies.

Please note that permission granted above only relates to the paper version of EQ-5D. Requests to use digital representations of EQ-5D (e.g. web, tablet, PDA) should be made separately to userinformationservice@euroqol.org attaching your initial registration.

Please find attached the UK English EQ-5D-3L version (word format). A brief user guide is downloadable from the homepage of the EuroQol website (www.euroqol.org).

Kind regards,

Nalinie Banarsi

Office Assistant

EuroQol Group Foundation

Appendix 9

Invitation letter to interviews

UNIVERSITY OF LEEDS

School of Healthcare
Baines Wing
University of Leeds
Leeds
LS2 9JT

Dear

I am writing to invite you to take part in a study of patient's experiences of their treatment as part of the Barnsley Irritable Bowel Syndrome Cohort Study.

The study involves a 1 -1 ½ hour interview with Emily Peckham a PhD student at the University of Leeds. During this interview you will be asked about the treatment you received and whether you found it helpful. We are interested in your experiences whether you found the treatment helpful or not, see the enclosed information sheet for further details.

The interviews will be used to look at whether or not people found the treatment helped their irritable bowel symptoms and general health and what, if anything it was about the treatment that helped or didn't help.

If you decide that you are happy to take part in the study, please sign the enclosed Consent Form and Contact Information Form and send them back to the Emily Peckham in the prepaid envelope provided. If you have any queries please contact Emily Peckham at the address given or by email: hcejp@leeds.ac.uk, or phone 0113 3433201.

Thank you for sparing the time to read through this.

Yours Sincerely

Emily Peckham

Participant information sheet for interviews

UNIVERSITY OF LEEDS

Information Sheet

Interviews exploring patients experience of treatment for Irritable Bowel Syndrome (IBS).

- We would like you to take part in a research study. Before you decide, you need to understand why this study is being done and what it will involve for you.
- Please take time to read the following information carefully.
- Talk to others about the study if you wish.
- Ask us if there is anything that is not clear or if you would like more information.
- Take time to decide whether or not you wish to take part.

Thank you for taking the time to read this.

What is the purpose of the study?

We are conducting interviews to find out if people receiving treatment found it helped their IBS symptoms.

Who is doing the study?

Emily Peckham a PhD student at the University of Leeds will be carrying out the study.

Why have I been chosen?

You have been chosen because you have been receiving treatment for your IBS as part of the Barnsley Irritable Bowel Syndrome Cohort Study.

Do I have to take part?

No, it is up to you whether or not you decide to take part. If you do decide to be included you will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. If you do not wish to take part you can still remain in the Barnsley Irritable Bowel Syndrome Cohort Study. A decision not to take part will not affect any of the care you receive now or in the future.

What will be involved if I take part in this study?

- You will be asked to attend one interview which will last 1 -1½ hours either in your home or another mutually convenient location. Unfortunately we do not have funds to reimburse travel expenses.
- We will ask about the treatment you received at Barnsley hospital. We are interested in whether or not you found the treatment helpful, what was helpful/unhelpful about the treatment, did you feel the treatment worked (or not)?
- There are no right or wrong answers. We just want to hear about your experiences, whether you found the treatment helpful or not.
- We will ask you if we can record the interview.
- The recording will be downloaded onto a computer and typed up.

We will be asking questions about your expectations about the treatment you received and your views and experiences of receiving it.

What do I have to do?

If you would like to take part in this study you need to complete and return the enclosed consent form and contact details form to **Emily Peckham** at the **School of Healthcare, Baines Wing, University of Leeds, LS2 9JT or by e-mail hcejp@leeds.ac.uk**.

What are the possible benefits of taking part?

There are no benefits to you personally however data gathered from this study may be used in the future to help people with IBS.

What are the disadvantages of taking part?

You will have to make time to attend the interview.

Can I withdraw from the study at any time?

Yes. Your participation is voluntary and so you can withdraw (i.e. tell the researcher that you do not want to take part) at any time without giving a reason. A decision to withdraw at any time, or a decision to not be included in the study, will not affect the standard of care that you receive.

Will the information I give be kept confidential?

Yes. All information that you give us will be kept strictly confidential. Your name will not be mentioned in any reports. You will be given an identification (ID) number and your interview responses will be stored on a secure server accessed by a password – protected computer using this ID number instead

of your name. Only the researchers at the University of Leeds will be able to link your name to your ID number. Your contact details linking you to your ID number will be destroyed three months after the end of the study.

Very occasionally, there may be a concern that a participant or someone they know is at risk. In this situation it may be necessary to pass on information to someone outside the research team. We would let you know if we were going to do this.

What will happen to the results of the study?

The results of the study will be presented at conferences and submitted to a scientific journal for publication. We expect this to happen within 6 months of the end of the study. We will also write a short report for all participants and this will be sent to you. Results of this study may also be used in teaching. You will not be identified in any reports or publications.

Who has reviewed the study?

The study has been reviewed by Leeds (Central) Research Ethics Committee.

Contact for further information

Emily Peckham, Baines Wing, School of Healthcare, University of Leeds, LS2 9JT
Email: hcejp@leeds.ac.uk

Thank you for taking this the time to read this information sheet.

Please keep this copy.

What to do now

If you **do not** want to take part – do nothing

If you **do** want to take part - complete:

- The consent form
- The contact details form

Then post them in the prepaid envelope provided.

Consent form for interviews

UNIVERSITY OF LEEDS

Participant Consent Form

Patients experiences of treatment for IBS

The participant should complete the whole of this sheet himself/herself

	Please confirm the statements by putting your initials in the box below
I have read and understood the participant information sheet	
I have had the opportunity to ask questions and discuss this study	
I have received satisfactory answers to all of my questions	
I have received enough information about the study	
I understand that I am free to withdraw from the study:- 1 At any time 2 Without having to give a reason for withdrawing.	
I understand that any information I provide, including personal details, will be confidential, stored securely and only accessed by those carrying out the study.	
I understand that my interview will be audio-recorded	
I understand that any information I give may be included in published documents but my identity will be protected by the use of pseudonyms	
I understand that relevant sections of data collected during the study may be looked at by individuals from the University of Leeds, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
I agree to take part in this study	

Participant Signature ……	Date
Name of Participant	
Researcher Signature ……	Date
Name of Researcher	

Thank you for agreeing to take part in this study

Research Interview Safety Protocol (Home Visit)

Before the interview date:

- Emily Peckham (EP) to pre-arrange call-in/call-out system with contact person few days before each scheduled home visit, to ensure availability.
- Contact person will either be supervisor or another colleague/friend, who will also have this protocol.
- A sealed envelope containing details of the address to be visited, the name of the person, a contact phone number for that person will be given to the contact person prior to the interview.
- EP will e-mail the contact person with details of the time the interview is to commence, and therefore the time to expect the first phone call.
- Contact person to confirm receipt of this email by email or text.

Before starting the interview:

- On arriving at the address of the interview, EP will phone contact person to say visit is about to start, and agree a time when the interview should be finished.
- EP will explain to the interviewee before the start of the interview that the University insist on this call-in/call-out system, and that if the interview over-runs s/he will need to make a quick phone call.
- If the interview over-runs, EP will take a break and phone contact person to inform them, and to agree a second finish time.
- If, on arrival at the address, EP has any concerns re safety (location, environment, other persons at address, or interviewee), she will not proceed with the interview. Interviewee and contact person will be informed, EP will return to base, and attempt to re-schedule the interview at an alternative location.

After the interview:

- EP will phone contact person to inform them that she has left the house, at or before the pre-arranged time.
- Contact person to shred sealed envelope.

General points:

- EP will endeavour to do home visit interviews during the day /early evening, rather than later on in the evening, or at weekends.
- If EP is having trouble with their phone, or does not/cannot make the interview for some reason, or the interviewee cancels the interview, contact person should be informed as soon as possible. EP will continue to attempt to make contact until contact person confirms receipt of the message.

- In the very unlikely situation that EP is being held against their will, but is allowed to make/receive phone calls, researcher will used an agreed “code” phrase in the phone call with contact person: “OK, I should be back in Manchester by then”. In this event contact person will immediately phone the police.

In the event that researcher does not phone at the agreed time:

1. Contact to phone EP on mobile phone
2. If no response, contact will phone interviewee
3. If no response, contact to phone police to report EP missing, giving details of address, person interviewed, and car registration no.
4. If appropriate, contact/police to contact relative

Emily Peckham’s contact details

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Adapted from template produced by Sheila C Youngson, July 2005

Appendix 10

NHS

National Research Ethics Service

Leeds (East) Research Ethics Committee

Yorkshire and Humber REC Office
First Floor, Millside
Mill Pond Lane
Meanwood
Leeds
LS6 4RA

Telephone: 0113 3050166

09 December 2010

Dr Kapil Kapur
Consultant physician and gastroenterologist
Barnsley Hospital NHS FT
Gawber Road
Barnsley
S75 2EP

Dear Dr Kapur

Study Title: **A randomised controlled trial to evaluate the clinical and cost effectiveness of two adjunctive treatments for patients with IBS compared to usual care alone: A: Homeopathic treatment (consultation + homeopathic medicine) and B: Supportive listening + placebo tablet**

REC reference number: **10/H1306/73**

Thank you for your letter of 25 November 2010, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered at the meeting of the Committee held on 07 December 2010. A list of the members who were present at the meeting is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of

the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		
Summary/Synopsis		01 September 2010
Letter from Sponsor		24 August 2010
GP Consent HOM	1	24 August 2010
Letter from Statistician		01 September 2010
Referees or other scientific critique report		01 October 2010
Update Document		05 October 2010
Protocol	Final v2	24 August 2010
Questionnaire: IBS questionnaire		
Participant Consent Form: Health Questionnaire/ Consent		
Investigator CV		
Response to Request for Further Information		25 November 2010
Participant Information Sheet: Information sheet OBS	1	24 August 2010
Participant Information Sheet: Supportive listening for irritable bowel syndrome	2	24 November 2010
Emily Peckham's CV		02 September 2010
GP Consent form SC	1	24 August 2010
Invitation Letter OBS	1	01 September 2010
CARE empathy measure		
Invitation Letter SC	1	25 August 2010
Gantt Chart for HIBS trial		
Professor Kate Thomas's CV		
GP Consent form OBS	1	24 August 2010
Participant Information Sheet: Information sheet SC	1	24 August 2010
Participant Information Sheet: Homeopathic treatment for irritable	1	24 November 2010

bowel syndrome		
Participant Consent Form: Consent form Hom	1	24 August 2010
Participant Consent Form: Consent Form SC	1	24 August 2010
Participant Consent Form: Supportive listening for Irritable Bowel Syndrome	2	24 November 2010
Letter of invitation to participant	1	25 August 2007
Letter of invitation to participant	1	25 August 2010
GP/Consultant Information Sheets	2	24 November 2010
REC application		
Participant Information Sheet: Information sheet Hom	1	24 August 2010
Participant Information Sheet: Barnsley Irritable Bowel Syndrome Cohort Study	2	24 January 2010

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H1306/73 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

pp.

Dr Carol Chu
Chair

NHS
National Research Ethics Service

NRES Committee Yorkshire & The Humber - Leeds Central
Yorkshire and Humber REC Office
First Floor, Millside
Mill Pond Lane
Meanwood
Leeds
LS6 4RA

Telephone: 0113 3050127

01 July 2011

Ms Emily J Peckham
PhD student
University of Leeds
School of Healthcare, Baines Wing
University of Leeds
Leeds
LS2 9JT

Dear Ms Peckham

Study title:	**Experiences of adjunctive treatments for IBS. Qualitative interviews of patients receiving homeopathic treatment or supportive listening for IBS.**
REC reference:	**11/YH/0178**
Protocol number:	**n/a**

The Research Ethics Committee reviewed the above application at the meeting held on 17 June 2011. Thank you for attending to discuss the study.

Ethical opinion

The Committee explained to you that you had stated in the IRAS form that, due to the sensitive nature of IBS, interview topic areas will be outlined in the participant information sheet, but that this information was missing from the sheet. You noted this had been omitted from the PIS and that it should have been included.

Members explained to you that it would be best to keep audio-recordings until the end of your PhD rather than destroy them after three months. The Committee suggested that all original data should be kept until your PhD is awarded.

The Committee informed you that asking questions such as 'how would you describe your therapist' may lead to disclosure of malpractice or criminal activity. Members asked you to include in the PIS information about your obligation to break confidentiality should such an issue arise.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

1. The participant information sheet should include information about the topic areas that will be discussed in the interview with participants.

2. The PIS should explain the researcher's obligation to break confidentiality should the participant disclose malpractice, criminal activity or safeguarding issues.

3. The sentence addressing your supervisor should be removed from the PIS.

4. The consent form should include the following standard clause '**I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from [*company name*], from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.**' You may remove 'medical notes' if this is not relevant to your study.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering Letter		12 May 2011
Evidence of insurance or indemnity		10 September 2010
Investigator CV		12 May 2011
Letter of invitation to participant	1	14 April 2011
Other: CV - A Nelson (Supervisor)		14 April 2011
Other: CV - J Greenhalgh (Supervisor)		14 April 2011
Participant Consent Form: Consent Form	1	14 April 2011
Participant Consent Form: Contact Details	1	14 April 2011
Participant Information Sheet	1	14 April 2011
Protocol	1	14 April 2011
REC application		12 May 2011

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Dr Janet Holt stated that Miss Emily Peckham is a PhD student in her department, but that she has not been involved in the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

11/YH/0178	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Margaret L Faull
Chair

Email: nicola.mallender-ward@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

"After ethical review – guidance for researchers"

Copy to: *Mrs Rachel E de Souza, The University of Leeds*
Dr Mike Bramall, Research Governance Lead, Barnsley Hospital NHS Foundation Trust

NHS
National Research Ethics Service
NRES Committee Yorkshire & The Humber - Leeds Central
Yorkshire and Humber REC Office
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Meanwood
Leeds
LS6 4RA

Tel: 0113 30 50166
Fax: 0113 85 56191

14 November 2011

Ms Emily J Peckham
PhD student
University of Leeds
School of Healthcare, Baines Wing
University of Leeds
Leeds
LS2 9JT

Dear Ms Peckham

Study title:	**Experiences of adjunctive treatments for IBS. Qualitative interviews of patients receiving homeopathic treatment or supportive listening for IBS.**
REC reference:	**11/YH/0178**
Protocol number:	**n/a**
Amendment number:	**2**
Amendment date:	**29 September 2011**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
reminder letter	1	26 September 2011
Notice of Substantial Amendment (non-CTIMPs)		29 September 2011
Covering Letter		28 September 2011

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

11/YH/0178:	Please quote this number on all correspondence

Yours sincerely

p.p.

Dr Janet Holt
Chair

E-mail: marc.neal@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mrs Rachel E de Souza, University of Leeds*
Mr Michael Bramall, Barnsley PCT