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Can self-reported depression be helped by homeopaths?

A pragmatic cohort randomised controlled trial with qualitative interviews with patients.

Petter Viksveen

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

The University of Sheffield
Faculty of Medicine, Dentistry and Health
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Abstract

Introduction: Depression is a common health problem. Some patients seek help from homeopaths as a complement or an alternative to conventional treatment. This may be due to reluctance to using or insufficient effect of "talking therapies" or antidepressants, or side-effects of such drugs. Insufficient evidence exists to determine whether homeopathy is acceptable, effective and safe.

Aims: To evaluate the effectiveness of offering adjunctive treatment by homeopaths to patients with self-reported moderate to severe depression, and assess acceptability and safety.

Methods: A pragmatic cohort multiple randomised controlled trial design was used. One third who fulfilled inclusion criteria were randomly selected to be offered a course of treatment by a homeopath. The primary outcome was the Patient Health Questionnaire (PHQ-9), 6 months post-randomisation. An intention-to-treat analysis compared "Offer" and "No offer" groups. An instrumental-variables-analysis (IV) assessed effects of received treatment. Safety was assessed through patients'/practitioners' reports. Qualitative interviews were used to learn about patients' experiences.

Results: The full sample (n=566) was recruited. One third (n= 185) were randomly selected to the "Offer group" were offered treatment by a homeopath, 40% (n=74/185) accepted the offer of treatment. Four-hundred-and-fifty-eight (81%) responded to the 6 month questionnaire. At 6 months, the "Offer" group (ITT-analysis) reported lower PHQ-9 scores (mean 1.4, 95% CI 0.2, 2.5) compared to the "No offer" group (p=0.019), with a small effect size (*d*=0.30). Secondary analyses showed similar results. IV-analysis showed 2.6 points (95% CI 0.5, 4.7, p=0.018) lower depression scores for those who received treatment by a homeopath (medium effect size, *d*=0.57). Although 14 adverse events were possibly linked to the intervention, most were mild, none were life-threatening and all were transient. Themes developed from 46 qualitative interviews with 33 patients regarding their experiences included feeling listened to, supported and accepted during consultations, and as a result, opening up and coming to realisations. Some patients described improvement in their mood, wellbeing, energy and physical symptoms, others experienced little or no change, or felt worse.

Conclusion: These preliminary (6 month) results suggest that treatment provided by homeopaths for patients with self-reported depression is acceptable. The effect size (d=0.30) is comparable to "talking therapies"; however, wide confidence intervals preclude firm conclusions from being drawn. There was no evidence that treatment by a homeopath was unsafe. Analysis of 12-month results is now required.

Table of contents

1. Introduction

1.1 Aims of this thesis

The primary aim of this thesis is to assess the effectiveness of offering treatment by homeopaths for patients with self-reported depression. The secondary aims are to assess the acceptability and the safety of treatment provided by homeopaths, and to learn about patients' experiences with this treatment.

A number of issues need consideration in order to achieve these aims. These are briefly described in the following sub-sections and more in depth in chapters 2 (Depression), 3 (Homeopathy) and 4 (Methods).

1.2 Depression, homeopathy and research methods

Depression

Depression is a common health care problem which affects people of all age groups in all countries in the world (WHO 2008). It is one of the leading causes of burden of disease in the United Kingdom and worldwide. Most of us have someone in our family who has suffered from depression, or we may have experienced it ourselves. The characteristic low mood and indifference contribute to reduced quality of life, lowered feeling of wellbeing and decreased ability to perform daily activities at work and at home. Depression may be recurrent, it can become chronic and it is the most important risk factor for suicide.

Depression is responsible for considerable suffering and disability affecting not only individuals, but also their families, their education and work places, and society at large. It has serious personal health, social and financial consequences. Overall, depression contributes to one third of the costs of mental disease (Sobocki et al. 2006). The total annual costs of depression have been estimated to be about £ 7 to 9 billion in the UK alone (McCrone et al. 2008, Thomas & Morris 2003) and 118 billion Euro in Europe (Sobocki et

al. 2006). It is expected to become the leading cause of burden of disease in the world by 2030 (WHO 2008) and the costs of depression are expected to increase (NICE 2010).

Treatment of depression

Depression treatments recommended by NICE (2010) are provided by general practitioners, specialists and mental health professionals. Treatment most often involves the use of antidepressants and "talk therapies" such as cognitive behavioural therapy and interpersonal therapy. NICE has introduced a model of stepped care with recommendations for interventions at various stages of depression, depending on duration and severity of symptoms. Although many patients benefit from such treatment, some experience only partial or no benefit, unwanted side-effects, or they may be unwilling to use such treatment. Some of these patients choose to consult with practitioners of complementary and alternative medicine (CAM) such as homeopaths (Frass et al. 2012). Depression is one of the most common conditions in patients who consult with homeopaths (e.g. Becker-Witt et al. 2004, Relton et al. 2007).

Homeopathy

Homeopathy is provided within and outside the NHS. It is a CAM therapy which typically involves consultations with a practitioner – a homeopath – who prescribes homeopathic remedies with the aim to restore health in patients. It was established by Samuel Hahnemann (1755–1943) and its main principle is the "Law of Similars" which suggests that "like cures like". The US National Library of Medicine MeSH definition (2015) explains that "Diseases are treated by highly diluted substances that cause, in healthy persons, symptoms like those of the disease to be treated." The use of highly diluted substances has been and is still subject to considerable controversy. Irrespective of this, patients continue to consult with homeopaths.

Homeopathy in depression: Research evidence

There is insufficient research evidence to draw conclusions on the effectiveness of homeopathy in depression (Pilkington et al. 2005). Evidence from uncontrolled studies suggests that patients experience clinically significant improvements (e.g. Adler et al. 2008,

Spence et al. 2005). However, such studies are limited by methodological weaknesses, including risk of bias. There is a need to determine the appropriateness of offering homeopathy to patients suffering from depression.

In addition to uncontrolled studies, a limited number of placebo-controlled double-blinded trials have been carried out to assess the *"efficacy"* of homeopathy in depression. However, such evidence is uninformative about a range of implementation issues and policy questions such as under what conditions the outcomes of trials can be replicated, and whether interventions are safe, effective and acceptable in routine practice. The comparability of existing homeopathy research evidence to commonly recommended interventions such as antidepressants and psychological and psychotherapeutic treatments will be discussed following an updated systematic review of homeopathy in depression (section 3.5.9 "Discussion of a systematic review of homeopathy in depression," under the heading "Homeopathy compared to other interventions for depression").

The need for pragmatic trials

The need to estimate the *"effectiveness"* of an intervention in real world clinical practice has given rise to practice based evidence from pragmatic RCTs. Such trials have high external validity as the tested intervention resembles treatment in routine healthcare (Thorpe et al. 2009). Pragmatic trials are better suited than explanatory trials to inform clinical practice decisions by patients, practitioners or policy makers (Thorpe et al. 2009, Tunis et al. 2003, Zwarenstein & Treweek 2009). No pragmatic randomised controlled trial (RCT) of individualised homeopathic treatment for depression has been carried out to date.

Meeting challenges in RCTs

There are a number of challenges involved in carrying out RCTs. An important one is ensuring that trials include sufficient numbers of patients, as it is difficult to draw firm conclusions based on underpowered trials. The number of included patients should therefore preferably at least match a pre-defined sample size calculation. Two issues are relevant to this end – recruitment and attrition. Patients invited to participate in RCTs may decline participation if they are aware that there is a chance that they will not receive the tested intervention. Patients might also drop out, either immediately after randomisation,

when they become aware that they have been allocated to the control group, or later on if they feel there is no improvement in their condition.

In order to try to increase recruitment rates and reduce attrition rates, the "cohort multiple" RCT (cmRCT) design (Relton et al. 2010) will be used. This involves random selection of eligible patients from an already established cohort of patients who have consented to be contacted again. Patients who fulfil inclusion criteria, but who are not randomly selected to receive the intervention, serve as a control group.

The need for qualitative studies

Some qualitative research has been carried out in order to determine patients' experiences with homeopathic treatment, but none assessing the experiences of patients suffering from depression. A qualitative study will be carried out to learn more from depressed patients' experiences with treatment provided by homeopaths.

Factors influencing choice of research methods

The choice of research methods in any research project is influenced by a whole range of factors. I have mentioned some reasons for carrying out the trial and the qualitative study described in this thesis. In research, important reasons for choice of research methods can include current gaps in research evidence, resources made available, and also researchers' past education and experience in research and their clinical experience. Researchers will have personal viewpoints and understandings of reality. This affects the researcher's choice of method and should be reflected upon and expressed prior to and during the planning of a research project. We will therefore take a look at ways in which my background, thoughts, beliefs, knowledge and understanding affected my choice of research method.

Who this thesis speaks to

This thesis is addressed to multiple audiences: patients with depression, clinicians treating depressed patients, homeopaths, homeopathy researchers and commissioners allocating funds for homeopathy and for depression treatment and research into these areas. The purpose of this thesis is to provide information on the effectiveness, safety and acceptability

of treatment by homeopaths for each of these audiences. This thesis has explored this research question in a UK NHS setting. However, the questions and answers will be applicable to these audiences in other settings and countries too.

1.3 Ontology and epistemology

This section discusses the issue of ontology and epistemology, as this is linked to choice of method. Ontology is here understood as described by e.g. Guba (1990): The question of what in nature we can know or what reality is. Epistemology is understood as the relationship between who it is who "knows" or "inquires" and what it is that is known or knowable, or how we can know.

My approach involves quantitative methods where the researcher's influence of the results should preferably be minimised; and qualitative methods where the researcher contributes more actively in the research process, for example through greater degree of interpretation of data. Such a "combined" approach can be considered to be pragmatic. I am taking a pragmatic theoretical perspective. In pragmatism researchers integrate quantitative and qualitative methods to answer the research question (Feilzer 2010).

I have a background as a practising homeopath in private clinical practice for 25 years. I have treated about 4,000 patients, of which about 100 patients consulted me for diagnosed depression as their primary complaint, and many more had self-reported undiagnosed depression. These patients had an average of 17 consultations with me at roughly one month intervals. My clinical experience, my education and the culture of my profession influence the way in which I view the intervention tested in this research project. The decision to carry out research assessing treatment provided by homeopaths for depression was motivated by my clinical experience with depressed patients, discussions with colleagues and from what I had learnt in the published research literature.

From a positivist viewpoint, my past clinical experience contributes to increased risk of bias. Therefore, a number of steps were taken to reduce the risk of bias, such as reducing the risk of selection bias through random selection of participants to the intervention and control groups, with random selection being carried out by a researcher not otherwise

involved in the trial; and reducing the risk of reporting bias by publishing the trial protocol prior to trial start (http://www.controlled-trials.com/ISRCTN02484593/ISRCTN02484593), by carrying out an intention-to-treat analysis, through other researchers checking data entry, and by reporting outcomes accurately and completely (including attrition and exclusions from the analysis, with reasons) to allow readers to consider reported findings.

From a more constructivist viewpoint the researcher's background, knowledge and experience can contribute to a greater extent in the research process (Postholm & Madsen 2006), rather than being a source of bias. This is particularly relevant in qualitative research, where researchers usually interact with participants to a greater extent than in RCTs.

My professional background with my theoretical knowledge and clinical experience, as well as my knowledge of and experience with research, was likely to contribute to the way in which I planned the research; the way I carried out qualitative interviews with patients; and the way in which I interpreted and reported the results of these interviews. Are there ways in which my prior my knowledge and experience could contribute to expand, rather than limit, my understanding and interpretation of qualitative data? As part of this, I have considered how I contribute to all stages of the research process, and how this can be a useful contribution to understanding patients' experiences, beyond my own current understanding of the field. These and related issues are dealt with in the methods, results and discussion sections describing the qualitative interview study.

The results of the trial and the qualitative study are compared and combined using a mixed methods approach. Mixed methods fit with the notion of pragmatism (Howe 1992, Tashakkori and Teddlie 2010). Positivist and constructivist views of reality can be seen as opposite standpoints where taking one particular viewpoint leads to the exclusion of the other. A pragmatic approach does not consider them as dichotomies, but rather as tools used in order to answer "real world" research questions (Feilzer 2010).

Human beings are complex. A pragmatic approach can aid me in developing the results of this research project, but I should be open to unexpected results and flexible in my approach. I need to be open to the fact that I might not be able to answer the original research questions; that other questions might be answered; and new questions developed.

We have in this chapter looked at the background and my line of reasoning for carrying out this research project, as well as my ontological and epistemological standpoint. In the following sections we will look at the prevalence, diagnosis, characteristics, comorbidities and consequences of depression, and how depression is commonly treated.

2. Depression

Depression is a common mental health problem. It can be associated with mental, physical and behavioural symptoms (NICE 2010). Depression is commonly characterised by a lack of interest or pleasure in doing things, or by a low mood (APA 2013). This may be described by patients as e.g. feeling "depressed", "down" or "blue", or "not being bothered with anything anymore." Accompanying symptoms can include for example tiredness, sleep and concentration difficulties, changes in appetite, and reduced self-esteem or self-confidence, even feeling worthless. Depression is associated with pessimism, social withdrawal, and thoughts or attempts of self-harm and suicide.

The degree and persistence of depression varies from patient to patient. Some experience variations during the day, such as feeling more depressed in the morning. Others feel depressed at particular times of the year and suffer from seasonal affective disorder (SAD), and women may experience depression after childbirth. Depression can be short-lived, episodic in nature or chronic.

Some patients are aware that they are depressed, others are not. They may be diagnosed with depression although they do not think they are depressed or they were not aware of it. Some patients consult with healthcare professionals, others do not. A British household survey showed that 54 % of depressed patients and 71 % of patients with mixed anxiety and depressive disorder had not consulted their GP (Bebbington et al. 2000). Similar figures were found in a UK household survey where 50 % of patients with a depressive episode and 85 % suffering from mixed anxiety and depressive disorder had not received any treatment over the past week (McManus et al. 2007). Depression is associated with stigma (Brohan et al. 2011, Latalova et al. 2014, Oakley et al. 2011, Want et al. 2007). A European survey showed that more than 20 % with depression or bipolar disorder had moderate or high degrees of self-stigma (Brohan et al. 2011). Self-stigma involves "taking on board" prejudice and feeling reduced personal value. Feeling embarrassed to admit depression to a health professional or being afraid of examination and treatment, or of being sanctioned, are some reasons why patients do not tell their GP (Meltzer et al. 2000). A large proportion of depressed persons believe that no one can help them and that they should be able to cope on their own.

Patients suffering from depression often have comorbidities. It is commonly associated with anxiety, but also with a wide range of physical conditions such as pain and obesity.

The following sections will focus on the prevalence of depression, how it is diagnosed and categorised, characteristics and comorbidities of patients affected by depression, consequences of and existing treatment for depression.

2.1 The prevalence of depression

Depression has become a considerable healthcare problem in many countries. According to the World Health Organization, over 150 million people in the world suffer from unipolar depressive disorder, with over 22 million citizens in Europe (WHO 2008). Depression has been ranked the third largest cause of disease burden worldwide and in Europe (WHO 2008). It is expected to become the leading cause of burden of disease worldwide by 2030. It is the most significant reason for years lost to disability, for both genders (WHO 2008, 2009a).

In the UK, depression is a common disorder and a considerable burden to individuals and society at large. According to the UK's leading mental health research, policy and service improvement charity, the Mental Health Foundation (2007) one in four UK citizens suffer from mental health problems every year and depression and anxiety are the most common problems.

Differences in estimations of the prevalence of depression may be due to variations in assessment methods and national differences. Examples include:

- Estimated lifetime prevalence of depression: from 4 – 10 % (Waraich et al. 2004) and 20 – 30 % (Kruijshaar et al. 2005)
- Six month prevalence rates in Europe: 7 % for major depression, 17 % for "depression" (Lépine et al. 1997)
- Point prevalence in the UK:
  - Major depression: from 2.1 % (Meltzer et al. 1995) to 2.6 % (Singleton et al. 2001)
  - Depressive episode: 2.3 %; mixed anxiety and depressive disorder: 9.0 % (McManus et al. 2007)

- Mixed depression and anxiety: 9.8 % (Meltzer et al. 1995)
- Depression symptoms: 11 % (Singleton et al. 2001)

Some authors point out that estimates may be too low due to recall bias (Patten 2003).

Depression continues to be a problem in South Yorkshire and the United Kingdom

In its health policy published over 20 years ago, the UK Department of Health (Carrington 1992) singled out mental illness as one of five priority areas. Main aims were reduction in suicide rates and improved health and social function for people with mental illness. The strategy included improved help for anxious and depressed patients (Jenkins 1994). Six years later, many of the goals had not been achieved (Department of Health 1998). The Mental Health National Service Framework published shortly after was more specific and more successful (Department of Health 1999, Appleby 2007). Over the last decade, strategies such as those presented by NICE (2010) have been further developed to fight depression and other mental health problems. However, many UK citizens still suffer from depression.

Results of a postal survey carried out in 2000 including more than 10,000 citizens in the Sheffield area showed that 7 % suffered from what could be categorised as depression (Coy et al. 2010). The Yorkshire Health Study (YHS), a population based sample recruited by GPs, funded by the Collaboration for Leadership in Applied Health Research and Care (CLAHRC), includes patients who have self-reported depression (Green et al. 2014). YHS data analysed in March 2012 showed that 26.9 % of 12,400 patients in South Yorkshire reported being moderately or extremely anxious or depressed, and over 9.4 % suffered from long-standing depression (Appendix 1: Viksveen et al. 2012).

Comparison of results from different studies must be done with caution as the methods of data collection and the definitions of depression vary. Nevertheless, we can conclude that depression continues to be a considerable health problem in the UK. In the following section we will look at how we can define and categorise depression.

2.2 Definitions and categories of depression

In this section we consider diagnostic systems used to categorise depression. This is of relevance in order to understand this group of patients and for consideration of outcome measures to be used in the pragmatic RCTs reported on in this thesis.

Two main diagnostic systems categorise and diagnose depression: *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-V) (APA 2013), an update of DSM-IV (APA 1994) and DSM-IV-TR (APA 2000); and the *International Statistical Classification of Diseases and Related Health Problems, 10th edition* (ICD-10) (WHO 2010). Very few changes were made for depression in DSM-V compared to DSM-IV/DSM-IV-TR.

The DSM-V depression categories most relevant to this thesis are: Major depressive disorder (single episode) (296.2x), Major depressive disorder (recurrent) (296.3x), and Persistent depressive disorder (300.4); and in ICD-10: Depressive episode (F32), Recurrent depressive disorder (F33), and Dysthymia (F34.1). Both diagnostic systems differentiate between mild, moderate and severe depression. Dysthymia is a form of low-grade depression that lasts for at least 2 years. Persistent depressive disorder covers both long-lasting low-grade as well as major depressive disorder in DSM-V.

There are considerable similarities between Major depressive disorder (recurrent and single episode) in DSM-V and Depressive episode and Recurrent depressive disorder in ICD-10. Both refer to: depressed mood, diminished interest and/or pleasure in daily activities, changes in appetite and weight changes, sleep disturbances (insomnia or hypersomnia), psychomotor disturbances (agitation or retardation), loss of energy or fatigue, feelings of worthlessness and inappropriate guilt (ICD-10 adds feelings of hopelessness), concentration difficulties (ICD-10 adds attention difficulties, DSM-V adds indecisiveness), suicidal thoughts (DSM-V adds thoughts of death other than fear, and specific plans or attempts to commit suicide). In both diagnostic systems symptoms should persist for 2 weeks.

The main difference between the two systems is that DSM-V criteria are more specific, whereas ICD-10 gives more room for wider interpretation. DSM-V specifies that either depressed mood or marked diminished interest or pleasure in (all or almost all) activities, as

well as at least 5 (of 9) specified symptoms, is present in Depressive episode or Recurrent depressive disorder. ICD-10 gives a broader description using terms such as "In typical […] depressive episodes […]" and referring to symptoms that are "[…] often present." For diagnosis of Severe depressive episode (without psychotic symptoms) ICD-10 refers to depression episodes with "several" symptoms.

This thesis mainly refers to DSM-V. A schematic overview of DSM-V diagnostic criteria for Major depressive episode (MDE) is given in table 1 (Major Depressive Episode – Diagnostic criteria according to DSM-V). For diagnosis of Major depressive disorder (MDD), a minimum of two Major depressive episodes (MDE) are required.

Table 1. Major Depressive Episode – Diagnostic criteria according to DSM-V

Major Depressive Episode			
Symptom	**Frequency/duration**	**Subjective**	**Objective**
Of the following symptoms:	**Min. 5 incl. 1 or 2** over 2 weeks		
1. Depressed mood	Most of the day Nearly every day	E.g. feels sad, empty	E.g. appears tearful
2. Markedly diminished interest or pleasure in all, or almost all, activities	Most of the day Nearly every day	Yes	Yes
3. Significant weight loss when not dieting or weight gain (> 5 % in one month) or decrease or increase in appetite	Nearly every day		Yes
4. Insomnia or hypersomnia	Nearly every day		
5. Psychomotor agitation or retardation	Nearly every day	Not only	Yes
6. Fatigue or loss of energy	Nearly every day		
7. Feelings of worthlessness or excessive or inappropriate guilt (may be delusional) (not merely self-reproach or guilt about being sick)	Nearly every day		
8. Diminished ability to think or concentrate, or indecisiveness	Nearly every day	Yes	Yes
9. Thoughts of death (not just fear of dying), or suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide	Recurrent		
Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning			
Exclude: - Symptoms due to general medical condition (e.g. hypothyroidism) - Symptoms due to physiological effects of a substance (e.g. drug of abuse, medication) - Hallucinations or Mood-incongruent delusions - Symptoms of Mixed Episode: Manic Episode + Major Depressive Episode, may be with psychotic features, for 1-week - Symptoms better accounted for by Bereavement, i.e. after loss of a loved one, for MDD the symptoms should persist for > 2 months or characterised by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation			

According to DSM-V, Persistent depressive disorder (PDD) involves depressed mood in addition to at least two symptoms including poor appetite or overeating, insomnia or

hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulties in decision-making, and feeling hopeless.

Symptoms in MDE, MDD and PDD should be present nearly every day, with the exception of the suicidal element of MDE/MDD which should be recurrent. Symptoms may be subjective, i.e. experienced by the patient (e.g. feeling sad) or observed by others (e.g. appearing tearful).

A range of diagnostic categories include depression as part of the symptom picture, such as Adjustment disorder with depressed mood, Adjustment disorder with anxiety and depressed mood, various types of Bipolar disorder and Alzheimer's disease accompanied by depression symptoms. These are not further commented on here, as the main focus of this thesis is unipolar depression.

We have looked at how depression is defined and categorised. In the following sections we consider if depression is more likely to occur in any particular patients groups.

2.3 Who is affected by depression? The epidemiology of depression

We will here consider if depression is more prevalent in particular groups of patients. We will focus on age, gender, socioeconomic status, ethnicity and patients' comorbidities.

2.3.1 Gender and age groups in depression

Unipolar depressive disorder represents a 50 % greater burden worldwide for women compared to men (Lépine et al. 1997, Lopez et al. 2006, Waraich et al. 2004, WHO 2008, 2009a, 2009b). Depression is the most significant cause of disease burden for women aged 15 to 44, in high-, middle- and low-income countries, assessed as disability-adjusted life-years (DALYs) (Waraich et al. 2004). European women suffer from depression more often than men (Lépine et al. 1997), and in the UK (McManus et al. 2007, NHS Health and Social Care Information Centre 2005). In the Yorkshire Health Study 62 % of participants with self-reported long-standing depression were female (Viksveen et al. 2012). Single and

divorced people living alone or with the sole responsibility of their children are more often depressed compared to others (Meltzer et al. 1995, Singleton et al. 2001).

Depression is common in all adult age groups in the UK. Some studies suggest it is more common in those under 55 (McDougall et al. 2007, McManus et al. 2007, Singleton et al. 2001), but figures vary from study to study. Extensive screening carried out for those aged 75 or above showed that 3.1 % suffered from severe depression, and 8.0 to 13.1 % had at least mild depression over the past week (Osborn et al. 2002). The Health Survey of England (NHS Health and Social Care Information Centre 2005) reported much higher frequency of depression in the elderly, ranging from 20 % to over 40 %. Others found prevalence rates in those aged 65 and above were 9.3 % in people living at home and 27.1 % in institutions (McDougall et al. 2007). The prevalence of depression decreased with age.

Overall, we can conclude that depression seems to be more common in women than in men, but it is a significant problem for both genders and in all age groups.

2.3.2 Socioeconomic status of for people with depression

Mental disease is more common in the poor and disadvantaged (Callan 2011, Mangalore et al. 2007, NHS Health and Social Care Information Centre 2005). The Health Survey for England showed that adults in the poorest fifth of the population are much more likely to develop mental illness compared to those on average incomes (24% vs 14%) (NHS Health and Social Care Information Centre 2005).

Mental disease is the cause and result of poverty and depression is particularly strongly related to it (Callan 2011). Deprivation accounts for almost 50 % of the variance in depressive disorder (Ostler et al. 2001). Unemployment increases depression rates (Jefferis et al. 2011), the prevalence is higher in deprived areas (Stafford & Marmot 2003). Some evidence suggests depression is more common in urban than rural areas (Ayuso-Mateos et al. 2001, Meltzer et al. 1995), other research shows the opposite (Probst et al. 2006).

We may conclude that mental health problems and depression is more prevalent in the more deprived parts of the population, and it is correlated to unemployment.

2.3.3 Ethnicity in depression

Prevalence figures for depression in ethnic groups in the UK vary from survey to survey. Minority ethnic groups are more likely than the average population to be diagnosed with mental health problems (http://www.mentalhealth.org.uk).

A systematic review has been carried to assess the prevalence of depression and anxiety in primary care comparing migrants/ethnic minorities to natives/ethnic majorities (Tarricone et al. 2012). The risk ratio for depression in ethnic minorities was 1.21 (95% CI 1.04-1.40, p=0.012), and non-significant for anxiety. However, studies were highly heterogeneous and the studies with larger samples and measures which are culturally adapted are needed.

Some authors found higher prevalence of mental health problems in individuals of non-British ethnic origin who experience unfair treatment at work and racial insults (Bhui et al. 2005). The Department of Health (2011) referred to a survey (McManus et al. 2007) which found a higher prevalence of common mental disease in women belonging to ethnic minority groups, in particular of South Asian origin (34%, compared to 19% in the white population), with no between group differences for men. Meltzer et al. (1995) similarly found a higher prevalence of depression in Asian/Oriental women, but not in men. Depression was less common in West Indians and Africans. In another survey depression was a less common reason for suicide in black African, black Caribbean and South Asian UK residents, compared to the white ethnic population (Bhui & McKenzie 2008). Ahmed and Bhugra (2007) point out that there is risk of under-diagnosing depression in ethnic minority groups due to language barriers and cultural differences.

In conclusion, there is some evidence to suggest that mental health problems in general and depression in particular may be more prevalent in ethnic minority groups compared to the overall population. However, more evidence is needed in order to clarify the question of prevalence of depression in particular ethnic groups.

2.3.4 Correlations between depression and other diseases

Major depression is more common in patients who suffer from chronic disease than those who do not (Katon 2003). Analysis of data from the WHO (2004) face-to-face questionnaire health survey using ICD-10 criteria for depression, carried out with more than 245,000 participants in 60 countries, showed that from 9.3 % to 23.0 % of patients with one or several chronic physical diseases suffered from depression (variations from country to country) (Moussavi et al. 2007). It was more common for someone with depression to suffer from physical comorbidities, than not ($p<0.0001$).

Systematic reviews and meta-analyses of longitudinal studies of patients diagnosed with major depressive disorder provide evidence for correlation between depression and specific physical diseases (Huijbregts et al. 2010, Penninx et al. 2013), such as heart disease (Klemenc-Ketis et al. 2010, Scott et al. 2013), migraine headache, asthma, cancer, osteoarthritis/rheumatic diseases and other chronic pain conditions (Klemenc-Ketis et al. 2010) and Alzheimer's disease (Xu et al. 2015). A survey including over 52,000 participants in 19 countries showed that depression is associated with heart disease (Scott et al. 2013).

In a Canadian study patients with long-term medical conditions were twice as likely to suffer from major depression (Patten 2001). The pooled risk of depression has been found to be 1.29 (95% CI 1.14-1.46) for cancer patients and 1.81 (95% CI 1.58-2.07) for heart disease, with hypertension, stroke, diabetes, Alzheimer's disease and obesity in-between these risk ratios (Penninx et al. 2013). The overall risk of mortality in depressed patients was 1.81 (95% CI, 1.58-2.07).

Anxiety is very commonly correlated to depression (Brown et al. 2001, Fava et al. 2000, Kaufman & Charney 2000, Thaipisuttikul et al. 2014). For example, anxiety was found in over 20 % of patients in a survey of patients with major depressive disorder (Thaipisuttikul et al. 2014), and over half of all depressed patients were anxious in two other studies (Fava et al. 2000, Kaufman & Charney 2000).

Some research suggests depression could be linked to physical age-related disease through reduction in leukocyte telomere length (Wikgren et al. 2012). Telomeres, which cover our

chromosomes, are shortened at each stage of cellular replication. This shortening ultimately results in cell death. Such explanatory models are at the initial exploratory stage. Another explanation, for which there is more substantial evidence, is that some chronic disease results from poor lifestyle habits, which are commonly seen in depressed patients.

In summary, there is considerable evidence for a correlation between depression and other healthcare problems such as anxiety, heart disease and chronic pain. The incidence of heart conditions increases with age. We will now consider correlations between lifestyle habits and depression.

2.3.5 Depression and lifestyle habits

Depressed patients are more likely to have unhealthy lifestyle patterns, including obesity, increased risk of smoking and eating disorders (Katon 2003, Luppino et al. 2010). A meta-analysis identified a reciprocal link between depression and obesity (Luppino et al. 2010). Data from the Yorkshire Health Study showed that 18.8 % were obese and 53.9 % were overweight or obese (Viksveen et al. 2012). Out of 802 obese patients, 34.5 % were moderately or extremely anxious or depressed (entire cohort 27.1%), and 15.1 % suffered from long-standing depression (entire cohort 9.3%).

Alcohol problems are much more common in depressed patients than in the overall population, and also more common than in patients with physical complaints such as hypertension, heart disease and diabetes (Sullivan et al. 2005). Estimates of prevalence of current alcohol problems in depressed patients ranged from 5 % to 67 % (median 16%), and lifetime alcohol problems from 10 % to 60 % (median 30%). Lifetime alcohol problems were more common in depressed patients (min. 16%, max. 40%), compared to the general population (min. 13%, max. 16%) (Grant & Hartford 1995, Regier et al. 1990).

A systematic review of longitudinal studies showed that smoking was a significant predictor for depression (pooled estimate OR 1.73, 95% CI 1.32-2.40, $p < 0.001$), and depression was a predictor for smoking (OR 1.41, 95% CI 1.21-1.63, $p < 0.001$) (Chaiton et al. 2009).

Overall, we may conclude that depression is correlated to lifestyle diseases such as obesity, and lifestyle habits such as alcohol abuse and smoking. Such lifestyle habits are also linked to lower socio-economic status.

2.3.6 The influence of depression on patients' quality of life and social life

Major depression is correlated with a higher degree of impaired function than most chronic diseases (Katon & Schulberg 1992). It typically results in considerable social impairment as depressed patients reduce social activities and rather withdraw and spend more time in solitude (NICE 2010). Patients suffering from depression experience considerably reduced quality of life, in part as a result of lowered mood and in part due to somatic symptoms and social withdrawal (Daly et al. 2010, Katon 2003).

2.3.7 The financial costs of depression

Depression is associated with significant financial costs for individuals, their families, employers and society at large. It includes direct costs such as expenses for medication, consultations and hospital in-nights, and indirect costs resulting from increased sick-leave and reduced productivity. Depression is associated with 50% increase in medical costs of chronic illness (Katon 2003). Expenses for treatment of depression in the UK have been estimated to be around £ 370 annually, with 84 % being spent on antidepressants alone (Thomas & Morris 2003). However, estimates including both direct and indirect costs add up to as much as £ 7 to 9 billion every year (McCrone et al. 2008, Thomas & Morris 2003). Depressed patients have been found to have reduced productivity and four times higher loss of work days compared to non-depressed patients (Lépine et al. 1997).

2.4 The most common forms of treatment for depression

Depression is correlated with a higher degree of use of medical services than most chronic diseases (Katon & Schulberg 1992). NICE recommended therapies primarily include psychological/psychotherapeutic treatment for minor to moderate depression, and antidepressant drugs for persistent and more severe depression (NCCMH 2010).

Psychological and psychotherapeutic treatments include e.g. cognitive behavioural therapy (CBT), counselling, interpersonal therapy, psychodynamic approaches, and couples/marital therapy. NICE recommends such treatment, in particular for mild to moderate depression, but points out that studies on which their recommendations are based, include a limited number of depression trials (NCCMH 2010).

Antidepressants are not recommended for sub-threshold or mild depression, due to a poor risk/benefit ratio. The use of antidepressants increased in the UK from 1993 to 2000 from 6.6 % to 17.5 % in women and from 4.8 % to 14.6 % in men (Brugha et al. 2004). The number of prescriptions of antidepressants in the UK almost doubled over the past decade, with about 55 million annual prescriptions (HSCIC 2014), on average almost one prescription was made for every UK citizen (HSCIC 2014), with similar figures for South Yorkshire (98.507 prescriptions per 100.000 inhabitants) (Sedghi 2014). In the Yorkshire Health Study 4.7 % reported using antidepressants, with 88.7 % of these patients being moderately or extremely anxious or depressed and 77.0 % reporting long-standing depression (data of 14.12.2011).

Estimates of the proportion of people with depression not using recommended treatments vary from 38 % to 85 % (McManus et al. 2007, NCCMH 2010, Singleton et al. 2001). A British household survey showed that 11 % of UK citizens with mixed anxiety and depressive disorder had used medication over the past week, 3 % used counselling or "talking therapy" alone, and 2 % used both medication and counselling (McManus et al. 2007). About 85 % did not use any form of treatment. Half of all those diagnosed with a depressive episode did not use any form of treatment. The remaining were divided between 25 % using medication, 8 % counselling or "talking therapy" alone, and 17 % using both.

There are many reasons why depressed patients may chose not to have medical or other treatment. They may have resistance to taking antidepressants, commonly due to fear of or experienced side-effects (Fortney et al. 2011, Layard 2006, Piguet et al. 2007), but also due to a general dislike of drugs (Layard 2006), experience of previous non-response to treatment (Fortney et al. 2011) or worry that they will become dependent on medication and losing control (Piguet et al. 2007). Some may feel a depression diagnosis as stigmatising or may fear negative impact on future healthcare insurance premiums. They may therefore decide not to consult with their GP.

2.5 The evidence base for different forms of treatment for depression

What is the evidence base for the different forms of treatment being used for depression, including those recommended by NICE? I carried out a search to identify systematic reviews assessing treatment of unipolar depression in adults published by the Cochrane Library. Although the Cochrane Library prides itself on being "the best single source of reliable evidence about the effects of health care" (The Cochrane Collaboration 2008), it has been criticised by some researchers (Edwards et al. 2001, Horsey 2002). Some authors, including Cochrane researchers, warn readers to be cautious when interpreting Cochrane reviews (Olsen et al. 2001). Nevertheless, the Cochrane Library can still be said to be a reliable source of high quality systematic reviews of health interventions. A full systematic review of the literature for depression treatments would require the use of additional databases. We will therefore now consider existing evidence from Cochrane reviews assessing the effectiveness of interventions used in depression for adults.

A search of the Cochrane Library for "depress*" in titles, abstracts and key words carried out on 04.07.2014 resulted in 423 Cochrane reviews. After removal of 359 non-relevant titles (not reporting on treatment of depression n=313, protocols n=30, prevention n=6, children & adolescents n=6, withdrawn n=4), 64 systematic reviews remained for the following areas:

- Antidepressants (n=35)
- Other types of medication (n=12)
- Psychological interventions (n=13)
- Psychological + pharmacological interventions, or collaborative care (n=5)
- Electroconvulsive therapy (ECT) (n=1)
- Complementary & alternative interventions (n=8)

Some systematic reviews reported on more than a single intervention.

2.5.1 Evidence for the efficacy of antidepressants

The two most commonly reviewed antidepressants are selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). These are also the two most

commonly prescribed antidepressants in the UK (SSRIs 53.6%, TCAs 27.8%) (HSCIC 2014).

SSRIs

Out of 18 Cochrane reviews of SSRIs, half reported on depression or dysthymia in general (table 2: Cochrane reviews of SSRIs in depression), whereas the other half assessed depression in sub-groups of patients (e.g. dementia, elderly or dialysis patients) (table 3: Cochrane reviews of SSRIs in depression for specific patient groups).

A single Cochrane review comparing antidepressants to placebo (Arroll et al. 2009) found that SSRIs were effective in a primary care setting. The review included only four trials assessing SSRIs and most were of short duration (6-8 weeks). Another Cochrane review assessed SSRIs for dysthymia, compared to placebo (Silva de Lima et al. 2005). SSRIs were superior to placebo with a median number needed to treat of 5 (95% CI 3.3, 9.0). There was however risk of bias in most trials and generalisability was limited due to heterogeneity of trials. A moderate and clinically significant effect of SSRIs was found for depressed diabetes patients, but results were limited due to risk of bias (Baumeister et al. 2012). There was weak evidence for the efficacy of SSRIs for depression in dementia (Bains et al. 2002), and a small effect for depression in coronary artery disease (Baumeister et al. 2011) and depression following stroke (Hackett et al. 2008). For depression in multiple sclerosis (Koch et al. 2011) and dialysis patients (Rabindranath et al. 2005) only a single trial was identified, thereby preventing any firm conclusions from being drawn.

The remaining Cochrane reviews assessing SSRIs, compared antidepressants to each other, and not with placebo or usual care (details in tables 2 and 3).

TCAs

Seven reviews assessed TCAs in depression or dysthymia in general (table 4: Cochrane reviews of TCAs in depression), with another six focusing on the efficacy of TCAs for depression in patient sub-groups (e.g. coronary artery disease and after stroke) (table 5: Cochrane reviews of TCAs in depression for specific patient groups).

Three Cochrane reviews compared TCAs to placebo in depression in general (Arroll et al. 2009, Furukawa et al. 2003, Moncrieff et al. 2004). All three reviews found TCAs were superior to placebo, but with risk of bias in most trials (Furukawa et al. 2003), studies were of short duration (Arroll et al. 2009), or the effect of TCAs was small compared to placebos mimicking antidepressant side-effects (Moncrieff et al. 2004). A single systematic review found TCAs were more effective than placebo in dysthymia, but results were limited by risk of bias (Silva de Lima et al. 2005).

Two Cochrane reviews found some effect of TCAs in elderly patients, although one review only found a difference at 24 months and not at 6, 12 and 36 months (Wilkinson & Izmeth 2012) and the conclusions in both were limited due to risk of bias (Wilkinson & Izmeth 2012, Wilson et al. 2001). A single review found a small effect of TCAs compared to placebo in patients suffering from depression after stroke, although results in all trials were limited by methodological weaknesses (Hackett et al. 2008). For depression in multiple sclerosis (Koch et al. 2011) and depression in coronary artery disease (Baumeister et al. 2011) only single trials were found, thereby preventing any firm conclusions from being drawn.

The remaining four Cochrane reviews compared the efficacy of TCAs with other types of antidepressants, and not to placebo or usual care (details in tables 4 and 5).

Several reviews suggest that all categories of antidepressant drugs carry a potential risk of unwanted side-effects (Arroll et al. 2005, 2009, Cipriani et al. 2005, 2009, 2010, Ferguson 2001, Furukawa et al. 2001, 2003, Khawam et al. 2006, Kirsch et al. 2008, Moncrieff et al. 2004, Nakagawa et al. 2009, NCCMH 2010, Omori et al. 2010, Rayner et al. 2010, Taylor et al. 2011).

Gelenberg (2010) states, that although progress has been made in treatment of depression, no major breakthrough has occurred over the last decade. According to existing evidence no category of antidepressants is helpful for all patients, and all categories carry a potential risk of unwanted side-effects. Peter Gøtzsche, leader of the Nordic Cochrane Center, stated that he believes antidepressants more often cause harm than benefits (Gøtzsche 2014).

Summary

In summary, evidence from one Cochrane review suggested SSRIs were more effective than placebo for depression in a primary care setting, and another review reported efficacy of SSRIs for dysthymia. For sub-groups of patients, efficacy of SSRIs for depression was found in single reviews for diabetes, and less convincing results for dementia, coronary artery disease and stroke. There was more solid evidence for the efficacy of TCAs compared to placebo for depression or dysthymia, and for some sub-groups of patients (elderly, coronary artery disease, stroke). The effect of TCAs was small when placebos mimicking antidepressants were used. There was, for trials included in reviews of SSRIs and TCAs, unclear or high risk of bias, heterogeneity of trials, and most trials were of short duration. Several reviews reported unwanted side-effects.

2.5.2 Evidence for the effectiveness of psychological therapies for depression

Sixteen Cochrane reviews assessed the effectiveness of psychological therapies for depression (Akechi et al. 2008, Barbato & D'Avanzo 2006, Baumeister et al. 2011, 2012, Churchill et al. 2013, Dennis et al. 2007, Hackett et al. 2008, Henken et al. 2007, Hunot et al. 2013, Lane et al. 2005, 2013, Orgeta et al. 2014, Rabindranath et al. 2005, Shinohara et al. 2013, Wilkinson & Izmeth 2012, Wilson et al. 2008). This included typical "talking therapies" such as cognitive behavioural therapy (CBT), psychotherapy, psychodynamic therapy, interpersonal therapy, marital and family therapy, counselling, motivational interviewing, problem solving therapy, behavioural therapy, as well as other psychological approaches such as relaxation, hypnosis and psycho-education.

Psychological therapies for depression in general

Out of 16 Cochrane reviews five reported on depression in general (Barbato & D'Avanzo 2006, Churchill et al. 2013, Henken et al. 2007, Hunot et al. 2013, Shinohara et al. 2013), whereas the remaining 11 reviews assessed depression in sub-groups of patients (cancer, heart conditions, diabetes, pregnancy, stroke, dementia, elderly patients) (table 6: Cochrane reviews of psychological therapies in depression).

The five Cochrane reviews assessing psychological therapies for depression in general included from 3 to 25 trials, reporting on a total of 144 to 955 patients. Results showed that psychological therapies were more effective than treatment as usual or waitlist controls. The largest systematic review (Shinohara et al. 2013) found that CBT was more effective than behavioural therapies, and there was little or no evidence that behavioural therapies were better than any other approaches. The authors of all five reviews pointed out that there were methodological weaknesses resulting from small sample sizes and/or risk of bias, including selection, performance, attrition, reporting and other forms of bias.

Psychological therapies for depression in sub-groups of patients

Four out of the 11 Cochrane reviews assessing psychological therapies for depression in sub-groups of patients, suggest that psychological therapies, compared to usual care, were helpful in reducing degrees of depression. This included patients suffering from incurable cancer (Akechi et al. 2008), coronary artery disease (Baumeister et al. 2011), diabetes mellitus (Baumeister et al. 2012) and dementia (Orgeta et al. 2014). The strength of all conclusions was however limited due to high or unclear risk of bias.

A systematic review assessing treatments for depression in elderly patients found that CBT was more effective than waitlist control and some active interventions, but no better than psychodynamic therapy (Wilson et al. 2008). Both in this review and in the following one, results were limited due to small trials and unclear or high risk of bias. Only two trials were identified in the second review of psychological therapy for depression in the elderly, suggesting little benefit from interpersonal therapy compared to antidepressants or to placebo medication alone (Wilkinson & Izmeth 2012). These trials were however small and had some risk of bias.

No evidence of benefit was found in psychological treatment for depression following stroke (Hackett et al. 2008), only a single trial could be included in a review assessing psychological treatment for depression during pregnancy (Dennis et al. 2007), and no trials fulfilled the inclusion criteria in the remaining three reviews (Lane et al. 2005, Lane et al. 2013, Rabindranath et al. 2005).

Summary

In conclusion, there is some evidence from Cochrane reviews to support the use of psychological interventions in depression in general and for some sub-groups of patients, but the strength of conclusions are limited as most studies have small sample sizes and there is high or unclear risk of bias.

2.5.3 Evidence for the effectiveness of collaborative care for depression

Collaborative care involves cooperation between healthcare professionals such as general practitioners, mental health specialists and others involved in patients' treatment and care, and can for patients for example involve medical treatment using antidepressants as well as consultations with a mental health practitioner.

A single Cochrane review assessed the effectiveness of collaborative care for depression and anxiety (Archer et al. 2012). A total of 79 trials including a total of over 24,000 patients were identified, of which 93 % were assessments of depression alone or anxiety and depression, and 7 % assessed the effectiveness of collaborative care for anxiety alone.

Overall, the evidence suggested that collaborative care resulted in significant improvement in depression compared to usual care, on short (0–6 months) and long term (13–24 months), but not to the same extent over time periods of more than 2 years. The strength of conclusions were somewhat limited by some methodological weakness, in particular unclear or high risk of bias which was found in all trials.

In conclusion, there is evidence from a single Cochrane review to suggest collaborative care is more effective than usual care, at least for treatment periods of up to two years, although all trials had risk of bias.

2.5.4 Evidence for other forms of treatment for depression

Ten Cochrane reviews reporting on interventions other than antidepressants and psychological therapies for depression were identified (Boer et al. 2005, Cooney et al.

2013, Dennis & Dowswell 2013, Jorm et al. 2008, Linde et al. 2008, Maratos et al. 2008, Rodriguez-Martin et al. 2001, Smith et al. 2010, Stek et al. 2003, Tuunainen et al. 2004).

Paraprofessionals

Some evidence suggested that paraprofessionals are more effective than no treatment, whereas there was insufficient evidence to conclude that the effectiveness of using paraprofessionals was comparable to using professionals for depression (Boer et al. 2005). Paraprofessionals may be patients themselves or lay people, and they may or may not be paid and under supervision of healthcare professionals such as psychologists, psychiatrists, social workers or nurses.

Exercise, relaxation techniques and music therapy

Exercise (Cooney et al. 2013) and relaxation techniques (Jorm et al. 2008) were found to be more effective than no or minimal intervention, but not more effective than psychological treatment. Only a small long-term effect was found for exercise and results were not statistically significant when assessing only trials with lower risk of bias. Music therapy was also found to reduce depression symptoms, but no firm conclusions could be drawn due to the low number of trials and high or unclear risk of bias (Maratos et al. 2008).

St. John's Wort

A Cochrane review including 29 trials found that St. John's Wort was superior to placebo and as effective as antidepressants (Linde et al. 2008). It also produced fewer side-effects than antidepressants. In spite of these promising results, NICE (2010) does not recommend practitioners prescribe it due to the risk of interactions with other drugs and uncertainties regarding appropriate dosage and contents of various products available on the market.

Acupuncture

Out of 30 studies included in a Cochrane review the majority found insufficient evidence of acupuncture compared to waitlist and sham (placebo) acupuncture in depression (Smith et al. 2010). A limited number of trials suggested acupuncture was beneficial as an adjunct to

antidepressants compared to antidepressants alone, and it was helpful for depression as a comorbidity to physical conditions. Conclusions were however limited by high risk of bias in most trials.

Various therapies for depression

Insufficient evidence was found to draw any conclusions on the effectiveness of electroconvulsive therapy for elderly depressed patients (Stek et al. 2003), transcranial magnetic stimulation for depression (Rodriquez-Martin et al. 2001), acupuncture, massage, light therapy and omega-3 fatty acids in antenatal depression (Dennis & Dowswell 2013). Overall, short-term light therapy was not found to be statistically better than antidepressants or sleep deprivation (Tuunainen et al. 2004). Short-term light therapy for depression was not found to be better than antidepressants or sleep deprivation (Tuunainen et al. 2004). Studies were heterogeneous and results of most studies were limited by risk of bias.

Summary

In summary, there was evidence to suggest the use of paraprofessionals, exercise, relaxation techniques, and to a limited extent music therapy, was more effective than no or minimal treatment, but not as effective as usual care (antidepressants and/or psychological treatment) or there was insufficient or no evidence for such a comparison. St. John's Wort was found to be superior to placebo and as effective as antidepressants, but has for safety reasons not been recommended by NICE for depression. There was overall insufficient evidence to support acupuncture, transcranial magnetic stimulation, and light therapy in depression, electroconvulsive therapy for depressed elderly patients, and acupuncture, massage, light therapy and omega-3 fatty acids in antenatal depression.

2.6 Depression remission and recurrence

Depression remission rates vary from nine to about 70 % (Byrne & Rotschild 1998, Rush et al. 2006). The problem of relapse in depressed patients has been an issue of discussion for more than two decades (Ramana et al. 1995). The severity of initial depression and concurrent comorbid illness serves as a predictor of future depression (Katon & Schulberg

1992) and patients with physical comorbidities have a poorer prognosis of depression (Huijbregts et al. 2010).

Up to three quarters of all patients with major depression suffer from recurrent episodes (Barbui & Cipriani 2009). Some authors recommend long-term use of antidepressants and psychotherapy for patients who are at high risk of recurrent depression (Thase 2006). Such treatment can go on for at least one year after remission. Others have however pointed out that patients who suffer from recurrent depression do not benefit as much from long-term treatment as patients with a single depression (Kaymaz et al. 2008). In a more recently published systematic review assessing depression after electroconvulsive therapy, authors concluded that although continuation treatment using antidepressants or electroconvulsive therapy was efficient, about half of all patients relapsed within one year (Jelovac et al. 2013).

2.7 Summary

We have in this chapter looked at how depression can be diagnosed and categorised, we have looked at the epidemiology and the consequences of depression, and potential treatments. Evidence was identified through Cochrane reviews that support the use of NICE recommended treatment such as antidepressants and some forms of psychological treatment, although the findings are limited due to unclear or high risk of bias in most trials. Although many patients improve significantly with the use of such treatment, many do not, suffer from recurrent episodes of depression, experience side effects or feel hesitant about using such treatments, in particular where there is risk of side effects. Many patients do not use recommended treatments (Bebbington et al. 2000, Collins et al. 2004) and up to three quarters of patients do not adhere to treatment (Poluzzi et al. 2013).

There are many reasons why depressed patients may chose not to have medical or other treatment. They may have resistance to taking antidepressants, commonly due to fear of or experienced side-effects (Fortney et al. 2011, Layard 2006, Piguet et al. 2007), but also due to a general dislike of drugs (Layard 2006), experience of previous non-response to treatment (Fortney et al. 2011) or worry that they will become dependent on medication and losing control (Piguet et al. 2007). Some may feel a depression diagnosis as stigmatising or

may fear negative impact on future healthcare insurance premiums. They may therefore decide not to consult with their GP.

There seems to be a clear need to improve the range, the effectiveness and the safety of interventions both for the treatment of depression and for preventing the recurrence of depressive episodes. NICE does not recommend any complementary or alternative forms of treatment such as homeopathy for depression. Nevertheless, such treatment is available both within and outside the NHS. In the following chapter we will look at homeopathy, one possible intervention for treatment of depression. Later chapters describe how treatment provided by homeopaths was tested for self-reported depression.

3. Homeopathy

In this chapter we will look at one of the forms of complementary and alternative medicine (CAM) most commonly used by people with depression in the UK, namely homeopathy. We will briefly explore what homeopathy is, how it can be defined, its prevalence of use and the existing research evidence, both for patients overall and in depressed patients in particular. For assessing the research evidence for the use of homeopathy in depression, a systematic review of the literature will be carried out.

3.1 What is homeopathy?

Homeopathy is a therapeutic modality which is currently practised in the UK, Europe and in most parts of the world (ECCH 2011, WHO 2001). It was developed by the German physician and chemist Dr. Samuel Hahnemann 200 years ago (Owen 2007).

Homeopathy involves a combination of consultations and prescription of homeopathic medicinal products (HMPs), as well as some underlying basic principles (Relton et al. 2008). The basic principle in homeopathy is the concept of treating "like with like" (Fisher 2012). It suggests that a substance that causes certain symptoms in healthy people may cure the same symptoms in those who are ill. The second, and more controversial issue, is the dilute nature of HMPs (Fisher 2012). A process of serial dilution and succussion (shaking) is carried out to reduce risk of side effects. Products are in many cases diluted to such an extent that no molecules are left of the original substance. HMPs are registered within the European Union through a special simplified registration procedure due to their low level of active principles (The European Parliament and Council 2004).

In the original form of homeopathy, so-called "classical" homeopathy, a single homeopathic medicine is prescribed after an assessment of the patient's total symptom picture. Homeopathic treatment is holistic and individualised (Bell 2005, Givati 2015). That the treatment is individualised means that it is adapted or tailored to each individual patient. Homeopaths' holistic view involves assessing and treating the whole person, including physical, emotional, mental and spiritual symptoms and characteristics (Givati 2015).

The consultation with a homeopath

This section explores the similarities and differences between homeopathic consultations and sessions with commonly used "talking therapy" interventions. Homeopaths use the consultation to develop the patient's biography, which helps the practitioner to prescribe a homeopathic medicine (Kaplan 2001, Owen 2007, Roy 2002). Several authors acknowledge the potential role that the consultation with a homeopath may have in the patient's therapeutic process (Johannes et al. 2013, Kaplan 2001, Thompson & Weiss 2006, and Townsend 2002).

The most obvious similarity with talking therapies is the amount of time patients commonly are given by their homeopath to present their problems. A first consultation normally lasts from 90–120 minutes, with about 40 minute follow-up consultations (Launsø & Rieper 2005, Rowe & Bell 2007, Steinsbekk 1999). This is considerably more than GP consultations which in the UK last about 12 minutes on average (The Information Centre 2007) and it is more comparable to talking therapy sessions with e.g. psychologists (NHS 2015). Patients are commonly seen again by their homeopath after three to four weeks and usually have about three to six consultations, whereas psychologists commonly see their clients more often.

Homeopaths are typically taught to be "good listeners" and "unprejudiced observers", skills which resemble two of psychologist Carl Rogers' key qualities of the therapist, namely "empathic understanding" and "unconditional positive regard" (Kaplan 2001, Townsend 2002). Rogers considered these as some of the core conditions to be necessary and sufficient to enable therapeutic change. Empathy has been found by others to be important for establishing the patient-practitioner relationship in the first stages of homeopathic treatment, although some research suggests it does not have a significant impact on patients' longer-term outcomes, including their main complaints and their general feeling of well-being (Bikker et al. 2005, Mercer 2005). A positive relationship between patients and their homeopaths is however important in order for the patient to feel free to disclose past painful experiences. Such disclosure, which is commonly aimed for in "talking therapies," may contribute positively to patients' mental state of health (Thompson and Weiss 2006).

Moreover, the extent to which patients experience enablement, their ability to understand and cope with their illness, as a result of seeing a homeopath, has been found to be positively correlated to patients' outcomes (Bikker et al. 2005, Mercer 2005). The degree to which this takes place in consultations with homeopaths, GPs, psychologists or other practitioners is likely to vary and depend on the practitioner, the patient and the patient-practitioner relationship.

There are also particular differences between consultations with homeopaths and sessions with e.g. psychologists. Homeopaths will to a greater extent than psychologists inquire about any symptoms or problems patients may experience, in particular patients' physical complaints (Johannes et al. 2013, Thompson and Weiss 2006). Homeopaths pose questions patients may not have been posed by other practitioners, such as whether they are warm-blooded, what food types they prefer to eat and whether they are affected by the weather. These questions may increase patients' self-awareness. This may affect their mental and overall state health and help patients understand that the mental and the physical are connected (Johannes et al. 2013), although this has not been found to be a prerequisite for patients' improvement (Thompson and Weiss 2006). Unlike "talking therapies" the goal of the homeopathic consultation is the prescription of a homeopathic medicine, to help support patients' self-healing abilities.

Further research is required to address the question: What changes in patients' state of health following homeopathic treatment are due to the homeopathic medicines, the homeopathic consultation, or the synergistic effects of different aspects of homeopathic treatment (Milgrom 2008, 2012, Thompson & Weiss 2006, Walach 2003, 2005)?

In summary, there are a number of similarities between consultations carried out by homeopaths and psychologists or other "talking therapy" practitioners, such as the time given to patients, practitioners' empathy, patients' disclosure of problems and enablement of patients. These elements may influence the patient-practitioner relationship and possibly also patients' outcomes. However, homeopathic treatment differs from psychological interventions in a number of ways, especially with regards to homeopaths' focus on all of patients' symptoms and complaints and the prescription of a homeopathic medicine.

Pluralistic practice

Homeopaths commonly apply a pluralistic approach to patients (Launsø & Rieper 2005). This means that they often recommend or prescribe additional supportive treatment such as dietary recommendations or other complementary and alternative therapies, either provided by themselves or by other practitioners. This is also the case in treatment of depressed patients, for whom homeopaths also may recommend for example counselling, psychotherapy or vitamins (Makich et al. 2007).

3.2 The prevalence of use of homeopathy in general and in depressed patients

A systematic review of population-representative 12 month prevalence surveys in 10 countries showed considerable variations in CAM use, ranging from 5 % to 75 % (Frass et al. 2012). Homeopathy was one of the four most commonly used CAM therapies. In another systematic review including 20 surveys in six countries, the prevalence of visits to a homeopath over the past 12 months was 1.5 % (range 0.2 – 2.9%), with UK figures ranging from 1.2 % to 1.9 % (Cooper et al. 2013).

A number of surveys indicate that depression is one of the most common problems patients consult homeopaths for, both within and outside the UK (Becker-Witt et al. 2004, Jacobs et al. 1998, Makich et al. 2007, Relton et al. 2007, Richardson 2001, Sevar 2000, 2005, Spence et al. 2005, Upham 2004, 2005, Valiant 2013, Viksveen & Steinsbekk 2005). In most of these surveys it is not clear whether patients had a medical diagnosis of depression, but they self-reported feeling depressed.

Homeopaths in the UK have carried out audits which showed that depression was among the five most common complaints seen in their practice (Sevar 2000, 2005, Upham 2004, 2005). In a university-hospital outpatient observational study including more than 6,500 patients treated over a 6-year period, depression was the sixth most common problem seen (Spence et al. 2005), whereas it ended up on 12th place in a smaller survey (Richardson 2001). Depression was among the most commonly treated symptoms in a survey including patients treated by 37 UK homeopaths who were members of the Society of Homeopaths (Relton et al. 2007).

Similar results have been found in studies in other countries. In Australia depression was among the five most common problems treated by homeopaths (Makich et al. 2007). A total population survey including more than 40,000 adults in a part of Norway showed that patients who were anxious or depressed were about twice as likely to have seen a homeopath compared to those who were not (Steinsbekk et al. 2008). In a clinic in another part of Norway, mental health problems were the third most common reason why patients consulted with homeopaths and depression was the most common mental health problem (Viksveen & Steinsbekk 2005). Out of 67 homeopaths in Denmark, Norway and Sweden, 96.5 % reported treating patients who suffered from depression (Valiant 2013). Depression was the second most common complaint seen by US homeopaths (Jacobs et al. 1998) and the 7th most common in men and 8th most common in women in a German survey including nearly 4,000 patients treated by 103 homeopaths (Becker-Witt et al. 2004).

We may conclude that depression is problem homeopaths are commonly consulted for within the UK and in other countries.

3.3 The overall evidence base for homeopathy

It is beyond the scope and relevance of this thesis to assess the overall evidence for homeopathy. A systematic literature search identified 263 published RCTs assessing homeopathy, of which most were placebo-controlled (n=217, 82.5%) not individualised (n=195, 74.1%), whereas fewer used controls other than placebo (n=46, 17.5%) and were individualised (n=68, 25.9%) (Mathie et al. 2013). Moreover, four in ten trials had been published in non-peer reviewed journals. This partly explains why only up to 110 trials assessing the effectiveness of homeopathy have been included individual systematic reviews assessing the effectiveness, safety and cost-effectiveness of homeopathy. A search of the Cochrane Library, EMBASE, MEDLINE and PubMed databases carried out in February 2015, as well as a search of my own archives, reference lists and requests sent to other researchers resulted in the identification of 123 systematic reviews of homeopathy (Appendix 2: Literature search results for systematic reviews of homeopathy).

Most of the identified systematic reviews (n=95) assessed the effectiveness of homeopathy in sub-groups of patients suffering from specific conditions, for example asthma, allergies and attention deficit hyperactivity disorder (ADHD), and some in sub-groups of patients (e.g. children) (n=4). Other reviews considered the effectiveness of specific homeopathic medicinal products (n=6) and particular ways of practising homeopathy (n=4). Three reviews considered the cost-effectiveness of homeopathy and four assessed adverse events.

The overall effectiveness of homeopathy was considered in 19 reviews, whereof one also considered the effectiveness for specific medical conditions, three assessed adverse events and one included economic evaluations.

Three reviews of systematic reviews of assessing homeopathy overall have been published in peer reviewed journals. One concluded that there was no overall strong evidence in favour of homeopathy (Ernst 2002), the second that there is clinical evidence supporting the effectiveness of homeopathy (Bornhöft et al. 2006), and the third found positive (but not convincing) results in most trials (Linde et al. 2001).

The existing reviews of systematic reviews provide conflicting evidence and it appears that no firm conclusion on the effectiveness of homeopathy can be drawn at this stage.

3.4 The safety of homeopathy

A single review of assessing published case reports and case series identified a number of adverse effects of homeopathy, some of which were serious (Posadzki et al. 2012). The reliability of this review has however been questioned by several authors (Johnson 2014, Tournier et al. 2013, Walach et al. 2013). Other published reviews suggest any side-effects following the use of homeopathic medicinal products are mild or moderate and transient, and not strong or persistent (Bornhöft et al. 2006, Dantas & Rampes 2000, ECCH 2009, Grabia & Ernst 2003, Pilkington et al. 2005, 2006, Woodward 2005). No interactions with conventional drugs have been reported. Another potential risk involves practitioners' recommendations to patients and delays in referral for necessary conventional examination and/or treatment. However, existing evidence suggests that such cases are rare (ECCH 2009, Posadzki et al. 2012).

In conclusion, there is widespread use of homeopathy; but conflicting evidence for the efficacy and effectiveness of the treatment, and there is no evidence to suggest it is not safe. Of those who seek homeopathic treatment, a significant proportion seeks treatment for depression.

3.5 Systematic review of homeopathy in depression

The following section will report on a systematic review carried out in order to assess existing research evidence for the safety, patients' outcomes, the effectiveness and the efficacy of homeopathy for patients suffering from diagnosed or self-reported depression, and their experiences during and after treatment. The background, aims, methods, results, discussion and conclusion will be presented.

3.5.1 Background for a systematic review of homeopathy in depression

A systematic review specifically assessing research evidence for homeopathy in depression was published nearly a decade ago (Pilkington et al. 2005). The authors identified three trials and six uncontrolled studies. Based on their findings they concluded that (p.158) "*[…] the evidence for the effectiveness of homeopathy in depression is limited due to a lack of clinical trials of high quality*." Few adverse events were reported in the identified articles and homeopathy was overall considered to be safe, although the authors pointed out that under-reporting of side effects was probable. No qualitative research assessing homeopathy in depression was identified. For the literature search, the authors used nine "conventional" databases, as well as six databases specialising on complementary and alternative medicine research, and they contacted homeopathy researchers. Now, 10 years later, an updated systematic review has been carried out and is presented as part of this thesis.

3.5.2 Aims of a systematic review of homeopathy in depression

The aims of this systematic review are to assess, for patients with diagnosed or self-reported depression; a) the safety of treatment provided by homeopaths; b) patients' outcomes during and after treatment provided by homeopaths; c) the effectiveness of

treatment provided by homeopaths; d) the efficacy of homeopathic medicinal products; and e) patients' experiences during and after treatment provided by homeopaths. Point a may be assessed using qualitative and quantitative studies; points b, c and d through quantitative studies and trials; and point e is assessed using qualitative studies.

These aims address the following questions:

a) Is treatment provided by homeopaths safe for patients with diagnosed or self-reported depression?
b) What are the outcomes of patients with diagnosed or self-reported depression during and after treatment provided by homeopaths?
c) What is the effectiveness of treatment provided by homeopaths for patients suffering from diagnosed or self-reported depression?
d) What is the efficacy of homeopathic medicinal products prescribed for patients suffering from diagnosed or self-reported depression?
e) What do patients with diagnosed or self-reported depression experience during and after treatment provided by homeopaths and what are their outcomes?

3.5.3 Methods used for a systematic review of homeopathy in depression

Search strategy

A total of 30 databases and other sources were used in order to carry out the literature search. The sources included 16 "conventional" databases: CINAHL, ClinicalTrials.gov, Cochrane Library, CSA (Sociological Abstracts), DARE, EMBASE, EU Clinical Trials Register, HTA, MEDLINE, NHS EED, PsycINFO, PubMed, Scopus, TRIP, Web of Science and Zetoc. Thirteen specialised CAM sources were searched: AMED, British Homeopathic Library (BHL), BMC Complementary and Alternative Medicine (BMC CAM), CAMbase, CAMEOL, CAM Quest, CCDAN, CORE-Hom, HomBRex-Database, Homeopathy Research Institute (HRI), IJHDR, Interhomeopathy and ReferenceWorks (complete information in Appendix 3: Databases and other resource website addresses for systematic review). Moreover, notifications about recently published research articles including the word "homeopathy" were regularly received from the National Center for Biotechnology Information (NCBI). Literature searches were carried out from 9 July to 12 August 2012, with update searches carried out on 15 November 2013. Search of a new

database (CORE-Hom) launched in 2014 was carried out on 16 March 2015. A second researcher (Philippa Fibert) checked all searches. A search builder was developed to define the most efficient search strings, defined as the shortest possible search string including the largest possible number of potentially relevant titles. The second researcher (PF) checked search strings and found them to be appropriate. Reference lists of relevant articles were checked and a list with identified relevant titles was sent to 44 researchers in 19 countries to check for additional titles.

Inclusion criteria were: studies reporting on homeopathic treatment of patients with diagnosed or self-reported depression. No language limitations were set. The time limit was set from 1982 to 2013 (CORE-Hom and NCBI notifications until March 2015) as it was not expected to find high quality studies published prior to this. Exclusion criteria included studies not assessing changes in patients suffering from depression as the primary complaint; bipolar disorder; homeopathic medicinal products (HMPs) used in anthroposophical medicine, administered as injections or in concentrations higher than 1:10,000 or one 100^{th} of the smallest dose used in conventional drugs (and therefore not available without a prescription in EU/EEA countries); animal studies; studies with less than 10 participants; short reports in conference proceedings; reports presented in books; studies not yet completed; and studies published prior to 1982.

Search strategies adapted to each database and information source included variations of the words "homeopathy," "homeopathic drugs," "potentised," "depression," "depressive disorder," "dysthymia" and "dysthymic disorder". Wildcard symbols including truncation (*) and single- (?) and multi-character wildcard symbols (* or $) were used as appropriate. The Boolean operators "OR" and "AND" were used to combine terms. The MEDLINE search strategy is included as an example (Appendix 4: MEDLINE search result).

Data extraction

Articles were translated where necessary. Data were collected, extracted, appraised and analysed. This was checked by the second researcher (PF). The first and second researcher's understanding of studies was compared to reach consensus. As consensus was reached there was no need to involve a third researcher. Results were reported separately for the safety of homeopathy, patients' outcomes during and after treatment provided by a

homeopath, the effectiveness of treatment provided by homeopaths, the efficacy of HMPs, and patients' experiences during and after treatment provided by homeopaths. Where appropriate, results were to be reported at an aggregated level, summarising results of more than one trial or study.

Data extracted from identified articles were inserted into a data extraction sheet, as suggested in the Cochrane Consumers and Communication Review Group's data extraction template (2013).

Data analysis

For data analysis, each individual research aim of this systematic review was addressed using evidence from particular research methods, as indicated below. Where relevant, risk of bias was assessed for each trial according to the Cochrane Collaboration's guidelines (Higgins et al. 2011). Reviews were not analysed, but solely used for identification of additional titles.

Safety of treatment

The safety of treatment provided by homeopaths for depressed patients should preferably be assessed using double-blinded placebo-controlled trials for determining any adverse effects resulting from the use of homeopathic medicinal products (HMPs) and pragmatic RCTs to consider adverse events following the entire "treatment package" which includes both consultations with a homeopath and the use of HMPs. It is more difficult to determine any causal relationship on the basis of other forms of evidence, such as cohort studies, case control studies and various types of uncontrolled studies. However, reports of adverse events following the use of conventional drugs are in almost one third of cases based on anecdotal case reports (Aronson et al. 2002). This is true in more than 80 % of the cases when assessing serious adverse events such as deaths following the use of conventional drugs (Onakpoya et al. 2015). More than one third of adverse events are based on RCTs, but most commonly these trials are too small to provide robust information about adverse effects resulting from conventional drugs. For this review, all titles included from the literature search were therefore used to consider the safety of homeopathy for patients with diagnosed or self-reported depression.

Patients' outcomes during and after treatment

Depressed patients' outcomes during and after treatment provided by homeopaths were assessed using uncontrolled observational studies (including case series and any other uncontrolled methods) and cross-sectional surveys. Studies were assessed according to the STROBE statement (von Elm et al. 2007).

Uncontrolled observational studies are less well suited for assessing the effectiveness of interventions than RCTs. The main reason for this is that RCTs by randomly allocating patients to the intervention and control groups in principle contribute to equally distributing known and unknown confounding factors. Results of uncontrolled observational studies carry a risk of significant effects of confounding factors on outcomes. In certain areas of research, it may not be feasible to use RCTs to test the effectiveness of interventions, and uncontrolled observational studies are therefore used instead. Results may then be assessed using either regression adjustment or propensity scores (Austin 2011). Such analyses take into consideration potential confounding factors and may thereby enable assessment of effectiveness of interventions. However, they can only be used to assess known and measured confounding factors. They do not deal with any unmeasured confounders. An example may be patients' expectations of the effect of treatment. Patients seeking treatment provided by homeopaths are likely to want to use such treatment. They may have past positive experiences with using homeopathy or someone else may recommend them to use it if they feel they experienced any benefits.

In this systematic review uncontrolled studies were therefore only used to assess outcomes during and after treatment provided by a homeopath. They were not used to provide evidence of any causal link between the treatment modality and the results patients report. Both patients and practitioners may very well have a perception of a cause-and-effect relationship between the treatment and the changes experienced by the patient or observed by the practitioner, but the lack of a control group precludes causal inferences from being made. Uncontrolled studies automatically have high risk of selection, performance and confirmation bias. Assessors could be a third person who was not otherwise involved in the study and unaware of what treatment that had been given, thereby reducing the risk of detection and confirmation bias. To avoid risk of attrition bias, uncontrolled studies should

provide all relevant information on outcomes. Moreover, information on all patients should preferably be included in the analysis or at least the number of excluded patients and reasons for attrition and exclusion should be reported. The risk of reporting bias could be reduced through means such as publication of a protocol prior to carrying out the study and the use of peer reviewers who have no vested interests.

For assessing patients' outcomes during and after treatment provided by homeopaths, risks of selection and performance bias were not considered, whereas risks of detection, attrition and reporting bias were considered. Other potential sources of bias and other methodological weaknesses were also considered, such as the size of studies, and whether studies were carried out prospectively (lower risk of bias) or retrospectively (higher risk of bias).

Effectiveness of the "package of care" provided by a homeopath

In order to determine the effectiveness of treatment provided by homeopaths (consultations and HMPs) for patients suffering from diagnosed or self-reported depression pragmatic RCTs could be evaluated. Pragmatic RCTs could include trials comparing treatment provided by homeopaths as an adjunct or an alternative to another intervention or an untreated or waiting list control group. Pragmatic RCTs automatically carry a risk of performance bias, as both patient and practitioner are aware of the treatment that is given. Other forms of risk of bias were assessed for each trial according to the Cochrane Collaboration's guidelines (Higgins et al. 2011).

Efficacy of homeopathic medicinal products

In order to assess the efficacy of HMPs for patients suffering from diagnosed or self-reported depression, evidence from blinded randomised placebo-controlled trials were used. Where p-values were reported, ≤ 0.05 was considered statistically significant. Risks of bias were assessed for each trial according to the Cochrane Collaboration's guidelines (Higgins et al. 2011).

Patients' experiences during and after treatment

Depressed patients' experiences during and after treatment provided by homeopaths were planned to be assessed using qualitative studies, using the Critical Appraisal Skills Programme (PHRU 2006) and by presenting results as a meta-synthesis.

Model validity assessed for all trials and studies

Model validity of studies, the degree to which the design and setting corresponds to "best practice" (Wein 2002), was assessed using recommendations put forward by Mathie et al. (2012). In order for a trial or study to be of high model validity it should be probable that experienced homeopaths would support the rationale for the intervention; the prescription of HMPs should be based on basic principles of homeopathy; practitioners should be qualified and experienced homeopaths; outcome measures should reflect the main effects that are expected of the intervention and it should be capable of detecting change (with no floor or ceiling effects); and the assessment period should be appropriate in order to detect the intended effect of the intervention.

3.5.4 Results of a systematic review of homeopathy in depression

This section presents the results of the literature search, as well as the analysis of identified research evidence answering each of the aims of the systematic review.

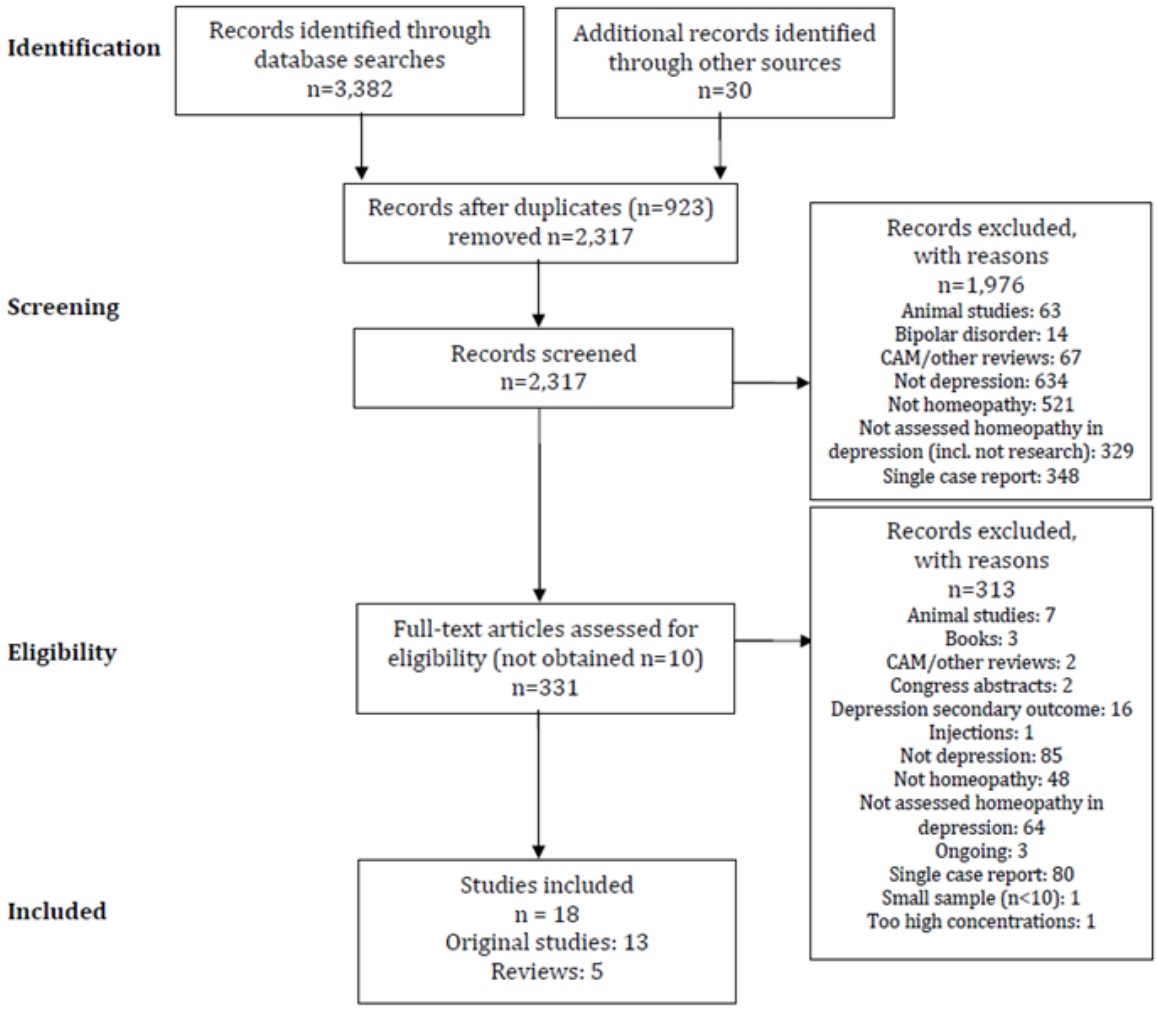
Literature search results

Thirty databases and other sources helped to identify 3,396 titles. After removal of duplicates and the addition of 30 titles identified through reference lists and contact with other researchers, 2,319 titles remained for screening. Results of the literature search are reported according to the PRISMA statement (Liberati et al. 2009) and presented in figure 1 (Flow of information for systematic review of homeopathy in depression). Fourteen original studies (Adler et al. 2008, 2011, 2013, Attena et al. 2000, Clover 2000, Dempster 1998, Macías-Cortés et al. 2015, Mathie & Robinson 2006, Oberai et al. 2013, Richardson 2001, Sevar 2000, 2005, Spence et al. 2005, Wasilewski 2004) and five reviews were

included (Davidson et al. 2011, Kirkwood & Pilkington 2004, Pilkington et al. 2005, Weatherley-Jones 2004, White 2009).

Ten uncontrolled studies including eight prospective observational studies (Attena et al. 2000, Clover 2000, Mathie & Robinson 2006, Oberai et al. 2013, Richardson 2001, Sevar 2000, 2005, Spence et al. 2005), a retrospective case series (Adler et al. 2008) and a retrospective survey (Dempster 1998) reported on depressed patients' outcomes following treatment by a homeopath. A single pragmatic RCT compared the effectiveness of a standardised homeopathic remedy compared to an antidepressant (fluvoxamine) (Wasilewski 2004). Three placebo-controlled double-blinded trials assessed the efficacy of HMPs in depression (all in conjunction with one or more in depth consultations with homeopaths), two comparing HMPs to placebo (Adler et al. 2013, Macías-Cortés et al. 2015) and the third assessing the non-inferiority of HMPs compared to an antidepressant (fluoxetine) using a placebo-controlled double-dummy method (Adler et al. 2011). No qualitative studies assessing depressed patients' experiences during and after treatment provided by homeopaths were identified.

Figure 1. Flow of information for systematic review of homeopathy in depression



3.5.5 Treatment provided by homeopaths: Is it safe?

The safety of treatment provided by homeopaths was assessed considering reported adverse events, side effects and deterioration of patients' state of health. All four RCTs (Adler et al. 2011, 2013, Macías-Cortés et al. 2015, Wasilewski 2004) and seven out of ten uncontrolled studies provided data relating to the safety of homeopathy (Adler et al. 2008, Clover 2000, Oberai et al. 2013, Richardson 2001, Sevar 2000, 2005, Spence et al. 2005). The remaining three uncontrolled studies did not provide any safety data (Attena et al. 2000, Dempster 1998, Mathie & Robinson 2006).

None of the trials and studies reported any serious adverse events. Such events may result in hospitalisation or prolonged hospitalisation, disability or limited ability for self-care, they may be life-threatening or result in death (NIH/NCI 2010).

Adverse events were reported in all three identified placebo-controlled double-blinded RCTs (Adler et al. 2011, 2013, Macías-Cortés et al. 2015). In Adler et al. (2011) adverse events were more common in the fluoxetine (21.4%) than the homeopathy (10.7%) group (difference p=0.275), more patients discontinued treatment due to adverse events in the fluoxetine (n=8) than the homeopathy (n=3) group (difference p=0.071), and a greater number of patients randomised to homeopathy (n=5) than the fluoxetine (n=1) group were excluded from the trial as a result of an intensification of depressive symptoms (difference p=0.207).

In the second placebo-controlled double-blinded trial the frequency of adverse events was similar in the homeopathy (19 of 30 participants, 63.3%) compared to the placebo (9 of 14 participants, 64.3%) group, with a mean number of adverse events of 1.23 per patient (37 adverse events) in the homeopathy group, compared to 1.07 (15 adverse events) in the placebo group (Adler et al. 2013).

In the third placebo-controlled double-blinded trial the frequency of adverse events in the homeopathy group was not significantly different compared to the placebo and fluoxetine groups (Macías-Cortés et al. 2015). Insomnia and dyspepsia were the most common adverse events, each occurring in six patients (13.6%) in the homeopathy group. Less common were nausea (n=5), fatigue (n=5), anxiety (n=4), dizziness (4), headache (n=3),

diarrhoea (n=3) and constipation (n=2). All adverse events were mild and tolerable. In addition, a so-called "homeopathic aggravation" was reported for 11.4 % of patients. Such a reaction involved an aggravation of patients' current symptoms, followed by clinical improvement. No patient in the homeopathy group needed to interrupt the treatment due to adverse events.

In a pragmatic RCT, a standardised HMP (Ignatia Homaccord) was better tolerated than an antidepressant (fluvoxamine), but no significance tests were presented (Wasilewski 2004). In the antidepressant group 55 % of patients reported nausea, 33 % stomach aches, and 18 % headaches, dizziness, shaking and indigestion. In the homeopathy group side effects were not reported by more than 10 % of patients. Two patients in the homeopathy group dropped out due to side effects, compared to 12 patients in the antidepressant group.

Out of the seven uncontrolled studies providing safety information, four did not identify any adverse events (Oberai et al. 2013) or deterioration of health (Richardson 2001, Sevar 2000, 2005) in a total of 204 patients. A slight deterioration was seen in one out of 14 patients (Clover 2000) and in two out of 201 patients (Spence et al. 2005). Adler et al. (2008) reported one out of 15 patients experiencing an intensification of depression in the fourth week of treatment, resulting in referral for conventional treatment with following improvement. In total, deterioration of health was reported in 4 (1%) out of 434 patients included in observational studies.

Underreporting of adverse events in uncontrolled studies seems probable as this was only found in 1 % of patients, compared to 10 % of patients in a pragmatic RCT (Wasilewski 2004) and 11 % in a double-blinded trial (Adler et al. 2011). Results of two placebo-controlled and one pragmatic RCTs suggested that homeopathic treatment was associated with fewer adverse events than antidepressants, although differences were either not statistically significant or no significance test was presented. A much higher frequency of adverse events (63%) in the third trial (Adler et al. 2013) is likely to have resulted from a more thorough reporting system and is unlikely to have resulted from the use of homeopathic medicinal products, as the frequency was the same for the placebo group.

Overall, the identified trials and studies showed only a limited number of adverse events or deterioration of patients' health and no serious adverse events were reported for patients

treated by homeopaths. There was no research evidence to suggest treatment provided by homeopaths for patients suffering from diagnosed or self-reported depression was not safe.

3.5.6 Depressed patients' outcomes during and after treatment provided by homeopaths

Patients' outcomes during and after treatment provided by homeopaths was assessed in 10 uncontrolled studies including a total of 529 patients (median 29, range 12-201) of which eight were prospective observational studies (Attena et al. 2000, Clover 2000, Mathie & Robinson 2006, Oberai et al. 2013, Richardson 2001, Sevar 2000, 2005, Spence et al. 2005), one was a retrospective case series (Adler et al. 2008) and the last one a retrospective survey (Dempster 1998). Details of the studies may be found in table 7 (Systematic review: Observational uncontrolled studies reporting on outcomes during and after treatment provided by homeopaths for patients suffering from diagnosed or self-reported depression).

The results of included uncontrolled observational studies

Uncontrolled observational studies were highly heterogeneous. Results can therefore only to a limited extent be summarised.

A prospective observational study included 24 patients suffering from depression who were treated with more than one homeopathic remedy at the time (Attena et al. 2000). After one year, more than half (54.2%) of the depressed patients reported marked improvement, one third reported moderate improvement, and the remaining 12.5 % were unchanged or worse.

A prospective observational study (Oberai et al. 2013) including 83 patients diagnosed with depression who received individualised treatment provided by homeopaths showed statistically significant improvements at three, six, nine and twelve months using the 17-point Hamilton Depression Rating Scale (HDRS) as the primary outcome measure ($p=0.001$). Statistically significant improvements were also found when assessing results with the Beck Depression Inventory (BDI) and the Clinical Global Impression (CGI-1) and Clinical Global Improvement (CGI-2) scales (all $p=0.001$). At 12 months marked improvement in HDRS scores (75-100%) was seen in 57.8 % (n=48), moderate

improvement (50-<75%) in 20.5 % (n=17), mild improvement (25-<50%) in 2.4 % (n=2), whereas 19.3 % (n=16) did not experience a significant change. Results were better for moderately and severely depressed patients, compared to those who suffered from mild depression.

The remaining six prospective observational studies (Clover 2000, Mathie & Robinson 2006, Richardson 2001, Sevar 2000, 2005, Spence et al. 2005) included 391 depressed patients (median 43, range 14-201) who were a subset of larger patient groups with various diagnoses. Patient-reported numerical rating scales showed at least moderate improvement (+2, +3 or +4 on seven- and nine-point numerical rating scales) in 50 % to 86 % of patients (median 67%), and slight or no improvement in 7 % to 50 % of patients (median 22%). No patients (Richardson 2001, Sevar 2000, 2005), one (Clover 2000) or two patients (Spence et al. 2005) reported slight deterioration. Deterioration was not reported in one study (Mathie & Robinson 2006).

Three of the six prospective uncontrolled observational studies assessed results after a mean of 2.4 (Sevar 2005), 3.6 (Spence et al. 2005) or 3.7 (Richardson 2001) consultations. Moderate (or more) improvement was in these three studies reported in 77.8 %, 53.2 % and 50.0 % of participants, respectively. Only Sevar (2005) reported on the length of the assessment period (mean 11 months, minimum 6 months). The remaining three studies (Clover 2000, Mathie & Robinson 2006, Sevar 2000) did not report the number of consultations or the assessment period.

A retrospective case series with 15 patients treated for depression (Adler et al. 2008) found statistically significant improvements on the Montgomery Åsberg Depression Rating Scale (MADRS) at the 2nd (mean 7 weeks), 3rd (14.5 weeks) and 4th consultation ($p<0.001$). However, only 5 (out 15) patients had outcomes at the 4th consultation. A minimum improvement of 50 % was found in 14 out of 15 patients at the 3rd consultation. The last patient was referred to an outpatient mental health clinic and was prescribed fluoxetine due to increased suicidal thoughts.

A single retrospective questionnaire survey including a random selection of 12 depressed patients (Dempster 1998) found patient-reported improvement in 85 % (IQR 55-90%, range 10-100%) assessed after at least 2 months and up to 3 years.

The strengths and limitations of included uncontrolled observational studies

All studies described the objectives of the study, the design, the setting, the participants, the sources of data, and the methods of assessment. With the exception of two studies (Attena et al. 2000, Dempster 1998) common terms were used in the title of the article indicating the study design. Most authors provided a reasonably informative and balanced abstract summary, although only to a limited extent in three studies (Attena et al. 2000, Sevar 2000, 2005) and one study did not provide an abstract at all (Dempster 1998). Exposures and outcomes were to a sufficient degree presented in all but three studies (Attena et al. 2000, Clover 2000, Dempster 1998). The majority presented an informative background and rationale for the study (Adler et al. 2008, Dempster 1998, Mathie & Robinson 2006, Oberai et al. 2013, Richardson 2001, Sevar 2005, Spence et al. 2005).

All studies referred to patients being diagnosed, but only two (Adler et al. 2008, Oberai et al. 2013) properly presented diagnostic criteria. The length of the study period varied considerably from study to study and in some cases also from patient to patient, ranging from 7 weeks or 3 consultations to one year or more.

Most studies were small, with six reporting on sample sizes of 30 patients or less (Adler et al. 2008, Attena et al. 2000, Clover 2000, Dempster 1998, Richardson 2001, Sevar 2005), three included between 50 and 90 patients (Mathie & Robison 2006, Oberai et al. 2013, Sevar 2000), and only one study had more than 200 patients suffering from depression (Spence et al. 2005).

All studies, with the exception of one (Oberai et al. 2013), included at recruitment all consecutive patients treated within a certain time period. Oberai et al. (2013) excluded patients who reported a 25 % improvement or more during a 1 week run-in placebo treatment period. Even though all patients were included at baseline, all studies had high or unclear risk of detection, reporting and attrition bias as assessors blinded to treatment type were not used in any of the studies, no pre-published protocol could be identified and there was insufficient information on drop-out patients and non-responders to questionnaires. Two studies had unclear or high risk of confirmation bias, one using a combined patient and clinician completed outcome measure (Sevar 2005) and the other with unclear reporting

procedures (Richardson 2001). The remaining studies had low risk of confirmation bias as outcomes were patient-completed.

With the exception of one study (Adler et al. 2008) reasons for drop-out were not or inadequately presented. Four studies provided insufficient information on how missing data was assessed (Dempster 1998, Mathie & Robinson 2006, Oberai et al. 2013, Richardson 2001) and in one study (Clover 2000) a high proportion of non-responders (45% in patients overall, proportion unknown for depressed patients) indicated high risk of attrition bias.

No study used regression adjustment or propensity scores to assess the effect of confounding factors. In two studies some measures were put into place in order to reduce any effects of confounding factors by avoiding concomitant depression treatment (Adler et al. 2008, Oberai et al. 2013). In four studies potential confounding factors or their potential effects were considered (Clover 2000, Mathie & Robinson 2006, Sevar 2005, Spence et al. 2005). In two studies researchers reported alternative explanations for clinical change in about 4 % (Mathie & Robinson 2006) and 5 % (Spence et al. 2005) of patients. In the total group of patients, of which depressed patients were a sub-group, 4 % also received acupuncture treatment in one study (Clover 2000). In another study no significant differences in results were found between patients who were only treated by homeopaths (n=375) compared to those who had some concomitant treatment (n=80) (Sevar 2005). The remaining four studies did not provide information on attempts to reduce or assess any potential confounding factors (Attena et al. 2000, Dempster 1998, Richardson 2001, Sevar 2000).

Eight out of 10 studies used outcome measures not validated for depressed patients. Two studies (Adler et al. 2008, Oberai et al. 2013) used established depression outcome measures (BDI, HDRS, MADRS), whereas the remaining studies used seven-point (Clover 2000, Mathie & Robinson 2006, Spence et al. 2005) or nine-point (Richardson 2001, Sevar 2000, 2005) numerical rating scales to assess changes, one assessed improvements in percent (Dempster 1998), and the last one as either marked or moderate improvement, or no improvement or worse (Attena et al. 2000).

The quality of the discussion section varied considerably from study to study, with only some (Attena et al. 2000, Clover 2000, Mathie & Robinson 2006, Oberai et al. 2013)

summarising key results with reference to objectives, discussing limitations more clearly and providing more cautious interpretations (Attena et al. 2000, Mathie & Robinson 2006, Richardson 2001, Spence et al. 2005). Only one study clearly discussed the generalisability of results (Mathie & Robinson 2006) and only three articles reported on funding sources (Adler et al. 2008, Mathie & Robinson 2006, Oberai et al. 2013).

Model validity was high for two studies (Adler et al. 2008, Oberai et al. 2013), low for one study (Attena et al. 2000), and of variable quality for six studies (Dempster 1998, Mathie & Robinson 2006, Richardson 2001, Sevar 2000, 2005, Spence et al. 2005). It was not possible to assess model validity in the last study (Clover 2000).

In summary, existing evidence suggests that somewhere between 50 and 85 % of patients reported at least a moderate improvement of their depression during and after treatment provided by homeopaths, whereas from 7 to 20 % did not report any change. Results from two studies assessing results after one year showed marked improvement in about 50 to 60 % of patients, whereas 13 to 19 % were unchanged or worse. Only two studies used validated outcome measures for depression, both identifying statistically significant improvements and more than half of the patients reported a marked improvement in their depression. Although results overall seemed promising, all studies had methodological weaknesses, mostly with small numbers of participants, unclear reporting of methods or results, and high or unclear risk of bias. Model validity was in most studies of variable quality.

3.5.7 The effectiveness of standardised homeopathic medication for depressed patients

The effectiveness of a standardised homeopathic remedy for patients suffering from diagnosed or self-reported depression was assessed in a single pragmatic RCT (Wasilewski 2004). Details of the trial may be found in table 8 (Systematic review: Pragmatic RCTs reporting on the effectiveness of treatment provided by homeopaths for patients with diagnosed or self-reported depression). Depression scores in 110 menopausal women who received a homeopathic remedy (Ignatia Homaccord, Heel GmbH) were compared to depression scores in 101 patients receiving fluvoxamine daily over a six-week period (Wasilewski 2004). Hamilton Depression Rating Scale (HDRS) score reductions were

comparable for the two groups (homeopathy 61 %, fluvoxamine 58%). Similar results were found for the Beck Depression Inventory (BDI). The authors claimed homeopathy was significantly better tolerated than fluvoxamine, but no significance tests were reported.

There was unclear risk of bias in the trial. Unclear risk of selection bias resulted from lack of information on random sequence generation and allocation concealment. There was unclear risk of detection bias, as there was no information on blinding of assessors. Although attrition rates were reported for both trial arms, there was unclear risk of attrition bias due to incomplete information on exclusions from the analysis. Insufficiently described research methods and the lack of a pre-published protocol or conference abstract contributed to risk of reporting bias. There was insufficient information in order to assess administration of the intervention and it is unclear if interim results were known which could affect the final results. No power calculation was reported and there was no information on comorbidities, length of consultations and details about practitioners. Some results were only provided as percentages and not as numbers. It is possible that an original language report could have provided more details, but such a report was not identified.

Model validity in this trial was unclear due to the lack of a rationale for the intervention, insufficient information to allow for judgment of whether the principles of the intervention was consistent with any existing principles of clinical practice, lack of information on the qualification and experience of practitioners, and insufficient information to assess if the follow-up period was sufficient to identify a clinical effect of the intervention.

In conclusion, evidence from a single pragmatic RCT suggested the effectiveness of a standardised homeopathic remedy was comparable to the effectiveness of an antidepressant. Depression scores were assessed using validated outcome measure and suggested about 60 % improvement over a 6 week period. However, no firm conclusions can be drawn due to methodological weaknesses resulting in unclear risk of bias and insufficient information to determine model validity.

3.5.8 The efficacy of homeopathic medicinal products in depression

The efficacy of homeopathic medicinal products prescribed for patients suffering from diagnosed depression was assessed in three RCTs, all in conjunction with one or more in depth consultations with homeopaths (Adler et al. 2011, Adler et al. 2013, Macías-Cortés et al. 2015). The three trials are here presented separately as the methods used are too different for results to be presented collectively. Further details may be found in table 9 (Systematic review: Placebo-controlled double-blinded trials reporting on the efficacy of homeopathic medicinal products used by patients suffering from diagnosed or self-reported depression).

The first RCT (Adler et al. 2011) was a non-inferiority placebo-controlled double-dummy trial with participants diagnosed with acute moderate to severe depression who received either an individually prescribed HMP together with a placebo for fluoxetine, or fluoxetine together with a placebo for the HMP. All patients underwent the same medical and homeopathic assessment. At 4 and 8 weeks the homeopathy group reported similar results (non-inferior) to those in the fluoxetine group as measured by the Montgomery Åsberg Depression Rating Scale (MADRS). Both groups (homeopathy n=48, fluoxetine n=43) improved over time ($p<0.001$), with no significant between group differences at 4 weeks (95% CI -6.95, 0.86, p=0.65) and 8 weeks (95% CI -6.05, 0.77, p=0.97). Remission rates were also comparable at both 4 weeks (homeopathy 47%, fluoxetine 55%, p=0.42) and 8 weeks (77% and 72%, p=0.72). Secondary outcomes including response and remission rates were assessed using non-parametric tests. Response rates (min. decrease of 50% in MARDS scores) were similar in the two groups at 4 weeks (fluoxetine 63.9%, homeopathy 65.8%) and 8 weeks (fluoxetine 84.6%, homeopathy 82.8%) (p-values not reported). Remission rates (MADRS score below 11) were also found to be similar between the two groups at 4 weeks (fluoxetine 47.2%, homeopathy 55.3%, p=0.422) and 8 weeks (fluoxetine 76.9%, homeopathy 72.4%, p=0.716). The trial had low risk of bias and model validity was high. The sample size was sufficient to establish non-inferiority of homeopathy compared to fluoxetine. No sample size calculation had been carried out, but non-inferiority was established with the first 59 patients at the trial pilot stage. No statistically significant between-group baseline differences were found. The main weakness of this trial was the high attrition rates (40%), but attrition rates and reasons for dropping out were similar in the two groups.

The second RCT (Adler et al. 2013) aimed to test the efficacy of HMPs compared to placebo, as well as the difference between an extensive (60-90 minute) and a shortened (30 minute) homeopathic consultation in moderate episodes (HAM-D score 17 to 24) of diagnosed acute major depression over a six week period (details in table 9). As only 44 (HMP n=30, placebo n=14) out of 228 patients were recruited, the number of participants was insufficient to allow for planned hypothesis testing (Adler et al. 2013). However, the authors provided a descriptive analysis of results which showed a large variance and heterogeneous data. No relevant differences in scores were found on the Hamilton Depression Rating Scale (HAM-D) or the Beck Depression Inventory (BDI) when comparing the two groups (HMPs vs placebo), or the full and shortened versions of consultations. Response rates, defined as an improvement in HAM-D scores greater than 50 %, were slightly better for HMP patients compared to placebo (OR 0.88), but with wide confidence intervals (95% CI 0.17; 4.58). The same was true for remission rates (HAM-D score < 8) with odds ratio at 3.95, but with 95% CI ranging from 0.90 to 17.45. Similar results were found when comparing the shorter with the more extensive consultation, but with results in favour of the shorter consultation (table 9). The trial had low risk of bias for comparison of HMPs to placebo, but high risk of bias for comparison of the extensive and the shortened consultation due to the impossibility of blinding the practitioner and the patient. The main weakness of the trial was that it was underpowered, thus making it impossible to draw any firm conclusions based on the results. Model validity was overall high, although it must be mentioned that patients were treated by a single practitioner, thereby reducing generalisability of results, and the trial did not aim to assess any long-term effects.

In the third double-blinded placebo-controlled RCT the primary aim was to compare the efficacy and safety of individualised homeopathic medicines with placebo for menopausal women suffering from moderate to severe depression (Macías-Cortés et al. 2015). All patients were diagnosed with depression according to DSM-IV. Each patient underwent a full consultation with a homeopath who prescribed an individually adapted homeopathic medicinal product. Following this, patients were divided into three groups, receiving either a) the homeopathic medicinal product they had been prescribed in C30 or C200 homeopathic potency (dilution), together with a placebo for fluoxetine (n=44); b) a placebo for the homeopathic medicinal product in addition to fluoxetine 20 mg (n=46); or c) a

placebo for both (n=43). All medication was taken twice daily. Patients were seen again at 4 and 6 weeks and did not receive any other treatment for depression. The main outcome measure, completed with assistance from a psychologist not otherwise involved in the trial and blinded to treatment arm, was changes in the 17-item Hamilton Depression Rating Scale (HDRS) scores from baseline to 6 weeks. An intention-to-treat analysis showed that improvements in the homeopathy group were significantly better compared to placebo with a 5.0 point difference in HDRS ($p<0.001$). Fluoxetine was better by than placebo by 3.2 points ($p<0.001$). NICE has considered a 3 point difference to be clinically significant (Kirsch et al. 2002). Analyses carried out with Bonferroni correction were also significant, both when comparing homeopathy and fluoxetine to placebo ($p<0.01$), whereas differences between homeopathy and fluoxetine were non-significant ($p=0.082$). Between-group differences in BDI scores were however not statistically significant ($p=0.130$). The authors suggested results of BDI scores could be biased as some patients had difficulties in understanding and responding to this self-reported questionnaire. Results measured using the Greene Climacteric Scale (GS), measuring vasomotor, somatic and psychological symptoms (including anxiety and depression), showed that homeopathy was superior to both fluoxetine and placebo ($p=0.002$).

In summary, the evidence of two placebo-controlled double-blinded trials suggested that homeopathic medicines were non-inferior to fluoxetine at 4 and 8 weeks and superior to placebo at 6 weeks, whereas no firm conclusions could be drawn in a third trial due to too low numbers of participants.

3.5.9 Discussion of a systematic review of homeopathy in depression

The effectiveness of databases and other sources for homeopathy literature searches

This systematic review includes 14 trials and studies assessing treatment provided by homeopaths for patients suffering from diagnosed or self-reported depression. It cannot be ruled out that additional titles could have been identified with the use of different search strategies. Nevertheless, this review adds 13 original research studies and trials to a previously published systematic review on homeopathy in depression (Pilkington et al. 2005). Eight (Adler et al. 2008, 2011a, 2013, Macías-Cortés et al. 2015, Mathie &

Robinson 2006, Oberai et al. 2013, Sevar 2005, Spence et al. 2005) out of these 13 studies and trials were published later or in the same year as the previous review. Four studies (Attena et al. 2000, Dempster 1998, Richardson 2001, Sevar 2000) were published prior to the previous review and were identified using additional databases and other sources. The last trial (Wasilewski 2004) was found through databases also used by the authors of the previous review and was therefore probably identified due to different inclusion criteria. Nine out of ten studies (10 out of 11 titles) included in the previous review did not fulfil the inclusion criteria used for this updated review, with five studies (six titles) (Awdry 1996a, 1996b, Davidson et al. 1995, 1997a, 1997b, Zenner & Weiser 1998) not reporting on changes in depression, two not assessing depression as the primary outcome (Thompson & Reilly al. 2002, 2003), a feasibility trial with too few participants (Katz et al. 2005), and a trial (Heulluy 1985) using products that were excluded in the updated review.

The use of a range of databases and other sources to identify homeopathy and other CAM research has previously been recommended by Cogo et al. (2011) and Pilkington (2007). However, in the current review all included articles were either found through the Scopus database (n=8), in reference lists (n=2), through contact with other researchers (n=2), in my own archives (n=1) or through NCBI notifications (n=1). Eight out of the 14 included titles were only found through a single source. Six of the titles were identified through nine "conventional" (CINAHL, Cochrane Library, EMBASE, MEDLINE, PsycINFO, PubMed, TRIP, Web of Science, Zetoc) and three "CAM specialized" (AMED, CAM Quest, CORE-Hom) databases, but all of these were also identified through Scopus.

Sixteen out of 30 sources did not produce any results that were included in this review (BHL, BMC CAM, CAMbase, CAMEOL, CCDAN, ClinicalTrials.gov, CSA, DARE, EU Clinical Trials reg, HomBRex, HRI, HTA, IJHDR, Interhomeopathy, NHS EED, Reference Works). Hence, for this review the use of the Scopus database, reference lists, other researchers, own archives and NCBI notifications would have been sufficient to identify all included articles. Although it is unclear whether this might be true for future reviews of this or other conditions treated with homeopathy or other CAM interventions, the effectiveness of used sources should be assessed in order to contribute to saving time and resources in future systematic reviews.

Single case reports – an unused source of data in homeopathy reviews

A total of 428 single case reports of homeopathic treatment of patients suffering from symptoms of depression were identified through the literature search. These reports were however excluded from the review. No previously published systematic reviews of homeopathy have assessed results of single case reports. Such reports are primarily produced by and for homeopaths who wish to learn more to inform their clinical practice (Thompson 2004). They provide only little and weak evidence that is of use in a research context. Moreover, assessing such a large number of reports would be considerably time consuming. However, inclusion of single case reports could be considered for a future review, in particular to be used for qualitative and safety assessment of the intervention.

Should various forms of homeopathy be analysed collectively or separately?

For this review, various forms of homeopathy were analysed collectively. Different forms of homeopathy such as "classical/individualised" and "non-individualised" homeopathy could have been assessed separately, as recommended in a recently published systematic review (Mathie et al. 2014). There are important differences between various homeopathy approaches, in particular involving longer consultations in "classical" homeopathy. Combining trials reporting on a variety of approaches may result in heterogeneity between trials, thereby preventing any meta-analyses from being carried out as well as difficulties in generalising results to "real-world practice". The current review mainly reports on studies and trials using a more "classical" or "individualised" approach to treating patients, with only one observational study (Attena et al. 2000) and a single pragmatic trial (Wasilewski 2004) using combinations of standardised treatment. Results of "classical" and other forms of homeopathy in this review did not differ considerably. Even if "individualised" homeopathy approaches had been assessed separately, studies and trials were still too heterogeneous for any meta-analysis to be carried out.

The safety of treatment provided by homeopaths

No evidence was identified that treatment by homeopaths for patients suffering from depression was unsafe. Only a limited number of adverse events were identified and none were serious. However, underreporting of adverse events was probable in uncontrolled

observational studies. For assessment of the severity of adverse events existing guidelines such as the Common Terminology Criteria for Adverse Events (CTCAE) guidelines (NIH/NCI 2010) should be applied.

Another issue mostly not addressed in uncontrolled studies was any potential risk arising from delayed referral of patients to GPs or other healthcare practitioners in situations where patients' health deteriorated or where there may have been risk of suicide and other forms of self-harm. Proper reporting systems are needed to assess and ensure patient safety. In one of the identified trials recent plans or attempts at committing suicide served as an exclusion criterion (Adler et al. 2011) and in another trial no patient reported any suicide ideation (Adler et al. 2013). In two double-blinded trials (Adler et al. 2011, Macías-Cortés et al. 2015) procedures for informing researchers about group allocation in the event of deterioration of a patient's health were put in place, but this was not needed for any homeopathy patient. In one observational study a single patient's mood deteriorated and was therefore referred for conventional treatment (Adler et al. 2008).

Adverse events are unfavourable and unintended symptoms that may or may not be related to the treatment (U.S. Department of Health and Human Services 2010, v.4.03). There is therefore a need to determine whether adverse events can be categorised as adverse effects, which may for example be done using the World Health Organization and Uppsala Monitoring Centre (WHO-UMC) system for assessment of causality (WHO-UMC undated). Otherwise, results may suggest a very high rate of adverse events unrelated to the intervention. This seemed to be the case in one of the placebo-controlled double-blinded trials which identified adverse events in more than 60 % of patients in both the homeopathy and placebo group (Adler et al. 2013). All trials found either that the rate of adverse events was lower in the homeopathy than the antidepressant group, although no statistically significant differences were identified (Adler et al. 2011, Wasilewski 2004), or the rate of adverse events following the use of homeopathy were similar to placebo (Adler et al. 2013, Macías-Cortés et al. 2015). It cannot be ruled out that trials were too small to provide any robust evidence of between-group differences in adverse events, as is common in research assessing adverse events of conventional drugs (Onakpoya et al. 2015).

Nevertheless, based on the existing evidence, homeopathic treatment was associated with only minor and transient adverse events and there was no evidence to suggest treatment was unsafe.

Uncontrolled observational studies – what do they tell us?

Uncontrolled observational studies are not well suited for providing valid and reliable information on the effectiveness of interventions. Self-selection to such studies can be assumed to be common, as most patients are likely to want to receive the intervention. This, together with the unavoidable lack of blinding of patients, practitioners and researchers, contributes to selection and performance bias.

The lack of a control group causes difficulties in interpreting whether any changes in patients may have resulted from the treatment or if these changes are the results of confounding factors, regression to the mean effects, seasonal or other forms of variations in depressed patients' state of health. In principle, regression adjustment or propensity scores could have been used in order to assess the effectiveness of homeopathy in uncontrolled studies, but this was not done. In more than half of the studies identified for this review other attempts were made to reduce or assess the effect of potential confounding factors. These factors seemed to have limited impact on results in those studies where they were assessed. However, several of the studies included patients with various types of complaints, and even where they provided baseline data that could have been used for assessing effectiveness of the intervention; they did not provide this information for the sub-group of depressed patients. Moreover, even in the cases where baseline data were provided for this particular group of patients, there would still be a risk of incorrectly assessing the effectiveness of the treatment due to unknown confounders. Therefore, instead of using uncontrolled observational studies to assess the effectiveness of treatment, it was decided to use them to assess changes in patients during and after receiving the intervention, with no claim made to any causal effects. It may still be of interest to readers to learn that about two out of three patients reported an improvement and 22 % felt only a slight or no improvement. Such knowledge may also contribute to planning future research including for example RCTs or qualitative studies.

Some measures that had been put into place strengthen the validity and reliability of results. Most uncontrolled studies used patient outcomes assessed in the absence of the practitioner, whether through the use of self-report postal questionnaires or with the assistance of a third person (e.g. researcher, assistant) not otherwise involved in the treatment of the patient, thereby contributing to reducing detection and confirmation bias. Including all consecutive patients treated over a pre-determined time period contributed to strengthening the reliability of results.

However, there were a number of weaknesses, many of which could have been avoided, that contributed to reducing the validity and reliability of results. No protocol had been published prior to carrying out the studies, thereby contributing to risk of reporting bias. Several studies had risk of attrition bias due to incomplete or lack of data on drop-out patients and missing data. Studies were mostly small, with more than half including 30 depressed patients or less and only two out of 10 studies used outcome measures validated for assessing changes in depression, thereby reducing the reliability of results. No study provided information on all aspects of the study, such as suggested in the STROBE statement (von Elm et al. 2007). This contributed to difficulties in fully assessing the methodological quality and model validity of studies.

Limited evidence for the effectiveness of standardised homeopathic remedies for depressed patients

Only a single RCT assessing treatment standardised homeopathic remedies for patients suffering from depression was identified (Wasilewski 2004). Although results suggested the product was as effective as an antidepressant used in the control group, the trial had several weaknesses and there was unclear risk of bias and unclear model validity. No firm conclusion could be drawn to determine the effectiveness of homeopathy in depression.

Limited evidence assessing the effectiveness of treatment provided by homeopaths for depressed patients

A placebo-controlled double-blinded trial comparing homeopathy to placebo (Adler et al. 2013) also included a (non-blinded) comparison of the effectiveness of shorter (30 minutes) and longer (up to 60 minutes) consultations. Although no significance tests could be carried

out, results suggested that shorter consultations (30 minutes) were more beneficial than a longer ones (up to 60 minutes), thereby suggesting that more time spent with a homeopath is not necessarily equated with better results.

The efficacy of homeopathic medicinal products for depressed patients

Three double-blinded RCTs were included in this systematic review (Adler et al. 2011, Adler et al. 2013, Macías-Cortés et al. 2015). In one of these three trials too few patients were recruited to allow for hypothesis testing (Adler et al. 2013). This was also the case in a fourth trial which could not be included in the review due to a too small sample size (n=6) (Katz et al. 2005). Problems with recruitment are common in clinical trials. A survey of trials carried out in primary care in the UK showed that two out of three experienced difficulties recruiting participants on time (Bower et al. 2007). Potential solutions to increasing participant numbers should be considered in future homeopathy research. One possible contribution to this may be the introduction of the cohort multiple randomised controlled trial (cmRCT) design (Relton et al. 2010) which will be further described in section 4.1.2 (The "cohort multiple" RCT design). Another factor limiting the number of recruited patients is extensive exclusion criteria in double-blinded trials. This may have been an important factor in the trial published by Katz et al. (2005).

The other two included trials had sufficient participant numbers for results to be analysed. In the first trial homeopathic medicinal products (HMPs) were found to be non-inferior to fluoxetine for depression at 4 and 8 weeks (Adler et al. 2011) and in the other trial HMPs were found to be superior to placebo and resulted in improvements that were statistically and clinically significant for depressed menopausal women at 6 weeks (Macías-Cortés et al. 2015). Both trials had low risk of bias and high model validity. The main weakness in both trials was that homeopathic treatment was carried out by a single practitioner, thereby to a limited extent reducing model validity and generalisability of results. In both trials results were assessed over a fairly short period of time. Although two placebo-controlled double-blinded trials provides only a limited amount of documentation for drawing firm conclusions as to the effect of homeopathic medicinal products used in depression, the existing documentation seems to be promising, at least when assessed over a shorter time period.

No pragmatic trials assessing treatment provided by homeopaths

No pragmatic RCTs assessing treatment provided by homeopaths for depressed patients, including consultations and homeopathic remedies, were identified. Very few pragmatic trials of homeopathy have been published for any clinical condition, with only 5.3 % (14/267) testing individualised treatment provided by homeopaths (Mathie et al. 2013). Most (217, 82.5%) were placebo-controlled and 32 (12.2%) were pragmatic trials testing standardised homeopathic products.

Homeopathy compared to other interventions for depression

This section compares the effectiveness, safety and acceptability of homeopathic treatment provided by homeopaths and the safety of homeopathic medicines, with widely used interventions for depression, including antidepressants and various forms of psychological treatments. Trials reported in the systematic review of homeopathy in depression presented in this thesis are here compared to research evidence for other interventions, in particular from Cochrane reviews.

The efficacy of homeopathic medicines compared to antidepressants

The efficacy of homeopathic medicines has been assessed through placebo-controlled double-blinded trials. Two such trials were identified in the systematic review (Adler et al. 2011a, Macías-Cortés et al. 2015) allowing for comparison with systematic reviews of antidepressants. Results are compared to two Cochrane reviews (Arroll et al. 2009, Moncrieff et al. 2004) and a recently updated overview of nine systematic reviews of antidepressants (Kirsch 2014).

The first placebo-controlled double-blinded homeopathy trial found homeopathic medicines were non-inferior to an SSRI (fluoxetine) at 8 weeks (Adler et al. 2011a). The second trial found a difference in favour of homeopathic medicines compared to placebo of 5.0 points using the Hamilton Depression Rating Scale (HDRS) at 6 weeks (Macías-Cortés et al. 2015). This was at least comparable to the difference between a selective serotonin reuptake inhibitor (SSRI) and placebo (3.2 points) that was tested in the same trial. These results were also similar for TCAs for depressed patients in general at 6 to 8 weeks (HDRS 3.2

points, 95% CI 2.4, 4.0) reported in a Cochrane review (Arroll et al. 2009). Moreover, results suggest a small effect size which were at least as good as for SSRIs (SMD 0.24, 95% 0.12, 0.35) (Arroll et al. 2009), TCAs in another Cochrane review (SMD 0.39, 95% CI 0.24, 0.54; sensitivity analysis 0.17, 95% CI 0.00, 0.34) (Moncrieff et al. 2004), and various antidepressants in a summary of nine systematic reviews (effect sizes 0.28–0.39) (Kirsch 2014). Only patients who are extremely depressed experience a clinically significant effect of antidepressants (Kirsch 2014).

Results of the two homeopathy trials suggest that homeopathic medicines may be at least as effective as antidepressants. Kirsch (2014) points out that the effects of antidepressants may be similar to that of placebos. Would this mean that homeopathic remedies only have placebo effects? This raises the question of what "placebo effects" are. Is it just the belief that a patient has received an active medication that results in an improvement? Patients participating in any placebo-controlled double-blinded depression trial are to a smaller or greater extent in contact with researchers and clinicians, and there is considerable interaction in trials testing individually prescribed homeopathic medicines. Such an interaction may considerably affect the participants. Parts of the changes experienced by patients may very well be the result of patients' belief that they have been given a medication, when they have in fact been given placebos, but health changes could also result from the interaction with the practitioner, leading to e.g. release of emotions or increased self-insight. Such effects, when intentionally achieved in psychotherapy or other "talking therapy" interventions, would normally not be referred to as "placebo" effects.

Only trials where patients have no consultation and just take a medication or a placebo could stand a chance of identifying a "placebo effect" if this effect is understood as patients believing they have been given an active medication. Only then would the placebo group not be influenced through the effects of the homeopathic consultation. Such trials cannot be carried out within the context of individualised homeopathic treatment, as this always involves a homeopathic consultation.

Hence, if homeopathic medicines are found to be equally effective to antidepressants, and antidepressants are found to have placebo effects, then this does still not answer the question of the extent to which the various aspects of the homeopathic treatment influence patients.

The effectiveness of treatment provided by homeopaths compared to psychological interventions

The effectiveness of treatment provided by homeopaths, including consultations and prescriptions of homeopathic medicines, is best assessed through pragmatic randomised controlled trials. No such trials were identified in the systematic review. It is therefore difficult to compare results identified through the systematic review of homeopathy in depression to the evidence for psychological interventions. A comparison of the results of "talking therapy" interventions with results of identified placebo-controlled homeopathy trials will nevertheless be made here.

Four Cochrane reviews reported on "talking therapies" for depression in general (and not for sub-groups of patients) (Barbato & D'Avanzo 2006, Churchill et al. 2013, Henken et al. 2007, Shinohara et al. 2013), of which only one (Barbato & D'Avanzo 2006) used outcomes that allowed for comparison with published placebo-controlled homeopathy trials. In addition, six systematic reviews of "talking therapies" for depression have been published on Medline over the past five years (Bolier et al. 2013, Cuijpers et al. 2010b, 2011, Driessen et al. 2015, Huntley et al. 2012, Linde et al. 2015).

The results of a single Cochrane review found a large standardised effect size of psychological interventions compared to no/minimal treatment (1.28, 95% CI 0.72, 1.85), but no significant difference between "talking therapies" and antidepressants (0.12, 95% CI -0.32, 0.56) (Barbato & D'Avanzo 2006).

Standardised effect sizes of various psychological interventions in non-Cochrane reviews ranged from small (0.14–0.42) (Bolier et al. 2013, Cuijpers et al. 2010b, Driessen et al. 2015, Linde et al. 2015) to moderate (0.52–0.67) (Cuijpers et al. 2010b, 2011, Driessen et al. 2015, Huntley et al. 2012, Linde et al. 2015), but typically with wide confidence intervals (ranging from about 0.0 to 0.9), when compared to waitlist, treatment as usual or placebo. Non-significant differences were found compared to antidepressants (Cuijpers et al. 2011), when comparing different forms of psychological interventions (Cuijpers et al. 2011), and for long-term results (3–12 months) (Bolier et al. 2013). Effect sizes were reduced from moderate to small when taking in to account publication bias, from 0.67 to

0.42 (Cuijpers et al. 2010b) and from 0.52 to 0.39 (Driessen et al. 2015), and authors pointed out that results were still likely to be overestimated due to risk of reporting bias.

These results suggest a small to moderate effect size of psychological interventions compared to usual care or waitlist controls, and little or no difference when compared to antidepressants. Results of two placebo-controlled double-blinded trials assessing homeopathic medicines for depression (Adler et al. 2011a, Macías-Cortés et al. 2015) suggested little difference compared to antidepressants and may therefore be comparable to the effectiveness of "talking therapy" interventions. A comparison between psychological interventions and the pragmatic trial presented in this thesis will be made in the "Discussion and conclusions" chapter.

Adverse effect of homeopathy compared to other interventions

Three placebo-controlled double-blinded trials (Adler et al. 2011a, 2013, Macías-Cortés et al. 2015) and a single non-blinded trial (Wasilewski 2004) included in the systematic review of homeopathy in depression reported adverse events. In the first placebo-controlled double-blinded trial (Adler et al. 2011a) the prevalence of adverse effects in the homeopathy group was lower (11%) compared to an SSRI (21%), although differences were not statistically significant. In the second trial (Adler et al. 2013) the frequency of adverse events was comparable to placebo; and in the third trial (Macías-Cortés et al. 2015) the prevalence of adverse events was comparable to both placebo and fluoxetine. In the non-blinded trial (Wasilewski 2004) the standardised homeopathic medicine was better tolerated than an antidepressant, with adverse events reported in up to 55 % of patients in the antidepressant group, compared to 10 % in the homeopathy group, and with a lower drop-out rate in the homeopathy group (1.9% vs 11.8%) due to side effects. All adverse events reported in homeopathy trials were transient and none were serious.

Adverse effects reported in Cochrane reviews range from no serious or severe adverse effects (Baumeister et al. 2012) in some subgroups of patients, to numbers needed to harm resulting in withdrawal from trials ranging from 4 to 30 for TCAs and from 20 to 90 for SSRIs (Arroll et al. 2009) for patients suffering from depression in general. Other authors have pointed out that TCAs may cause serious adverse effects such as seizures and severe cardiac symptoms resulting in death (Ferguson 2001).

Common side effects associated with SSRIs include weight gain, gastrointestinal symptoms (e.g. nausea), sleep difficulties, dizziness, headaches, lethargy, anxiety and agitation (Ferguson 2001, Kirsch 2014). Ferguson reports that although SSRIs generally are considered to be safer and cause fewer side effects than TCAs, SSRIs have been reported to cause sexual dysfunction in 55 to 75 % of patients included in clinical trials, and sexual dysfunction is seen in up to 92 % of patients for some types of TCAs. SSRIs have also been found to cause symptoms such as reduced serum sodium levels in elderly, which may result in seizures.

Current evidence therefore suggests that, compared to the existing evidence for antidepressants, homeopathic treatment may be associated with a comparable or lower rate of side effects, and resulting in no serious side effects.

The acceptability of homeopathy compared to other interventions

The acceptability of an intervention can be considered by assessing the proportion of patients agreeing to take up an offer of treatment (acceptance rate) and the proportion of patients dropping out due to adverse events or for other reasons (attrition rate). Each of these two aspects will here be assessed separately.

Two placebo-controlled double-blinded trials of homeopathy in depression (Adler et al. 2011a, Macías-Cortés et al. 2015) did not report acceptance rates, but recruited a sufficient number of patients for hypothesis testing. Another two trials (Adler et al. 2013, Katz et al. 2005) were unable to recruit a sufficient number of patients to enable statistical analyses. In one of these trials (Katz et al. 2005) 35 % of patients refused randomisation as they had a particular treatment preference and no patient stated not wanting to accept the offered intervention. It is not clear why 74 % of patients in the other trial were "not further interested after receiving more information about the study details" (Adler et al. 2013, p.6), but some of these patients may have turned down the offer due to the possibility that they might not receive the intervention. It is not uncommon that patients who are invited to participate in RCTs refuse randomisation, as they then risk not being offered the tested intervention (Torgerson & Sibbald 1998). The identified Cochrane reviews of antidepressants or other interventions did not report on the proportion of patients agreeing

to participate in the included trials. It is, due to insufficient information, not possible to compare acceptance rates for homeopathy and other interventions.

A single Cochrane review (Arroll et al. 2009) assessing the efficacy of antidepressants compared to placebo for depressed patients in general, found that numbers needed to harm (NNH) resulting in withdrawal from trials ranged from 4-30 for TCAs and 20-90 for SSRIs. A placebo-controlled homeopathy trial reporting on drop-outs resulting from adverse events had NNH of 88 for the homeopathy group, compared to fluoxetine (Adler et al. 2011a). Another trial found no drop-out due to homeopathy and a single patient (2.3%) dropped out in the fluoxetine group (Macías-Cortés et al. 2015). In a pragmatic trial of a standardised homeopathic medicine (Wasilewski 2004) a lower drop-out rate due to side effects was found for homeopathy (1.9%) compared to antidepressants (11.8%). These results suggest overall that homeopathic medicines were more acceptable to trial participants than antidepressants.

Three Cochrane reviews of psychological and other "talking therapy" interventions for depression in general provided data on attrition rates (Barbato & D'Avanzo 2006, Churchill et al. 2013, Shinohara et al. 2013). Barbato & D'Avanzo (2006) found a lower drop-out rate for marital therapy, compared to drug therapy RR 0.31 (95% CI 0.15 to 0.61). Churchill et al. (2013) found no significant difference between CBT and treatment as usual (RR 1.01, 95% CI 0.08, 12.30). In the third review, no differences were found between behavioural and other forms of psychological therapies (Shinohara et al. 2013). No pragmatic trial of homeopathy for depression was identified in the systematic review to allow comparison with psychological interventions. Assessment of the pragmatic homeopathy depression trial reported on in this thesis will be addressed in the "Discussion and conclusions" chapter.

Summary of homeopathy compared to other interventions for depression

In summary, limited existing research evidence suggests homeopathic medicines may be at least as effective as SSRIs and TCAs in treatment of patients suffering from depression, they may produce fewer and no serious adverse effects, and they may be associated with lower drop-out rates. Results of the pragmatic trial assessing treatment provided by

homeopaths presented in this thesis will be compared to antidepressants and psychological interventions in the discussion chapter.

3.5.10 Recommendations for future research

The reproducibility of trials showing that homeopathic medicinal products were non-inferior to antidepressants and superior to placebo in the treatment of depression should be tested. Pragmatic RCTs are needed in order to test the safety, effectiveness and cost-effectiveness of homeopathy. Such trials should preferably assess results over a longer period of time, comparators should preferably be specific interventions currently in use within the NHS or overall "treatment as usual", and exclusion criteria should be limited as much as possible in order to increase the generalisability of results to "real-world" practice.

Researchers carrying out uncontrolled observational studies should contribute to improve the validity and reliability by: a) Publishing protocols in order to reduce the risk of reporting bias; b) Using larger sample sizes and include all consecutive patients treated over a pre-determined period of time; c) Providing baseline data in order to allow for assessment of effectiveness of treatment by the use of regression adjustment or propensity scores to account for known potential confounding factors, or at least to discuss the influence of any potential confounding factors; d) Assessing patients' state of health using outcome measures validated for assessing changes in depression (e.g. HDRS or PHQ-9); e) Providing figures and reasons for drop-out and ways of dealing with missing data in order to reduce the risk of attrition bias; f) Using guidelines such as the STROBE statement to allow readers to assess the quality of studies; g) Ensuring high external or model validity by ensuring that treatment used is as similar to "real world practice" or "best practice" as possible.

Qualitative studies should be carried out to learn about depressed patients' experiences with treatment provided by homeopaths.

3.5.11 Conclusion of a systematic review of homeopathy in depression

A systematic review helped identify 14 studies and trials assessing treatment provided by homeopaths for patients suffering from diagnosed or self-reported depression. The existing evidence did not suggest that the treatment was not safe. Evidence from two single double-blinded placebo-controlled trials suggests that homeopathy may be non-inferior to antidepressants and statistically and clinically superior to placebo over a short (6-8 weeks) period of time. The results of 10 uncontrolled observational studies provided evidence suggesting that more than half of all patients receiving treatment provided by homeopaths may report at least a moderate improvement in their depression symptoms, but most studies had significant methodological weaknesses. More research is needed in order to learn more about the potential effects of treatment provided by homeopaths for patients suffering from depression, preferably by assessing long-term results and ideally with the use of RCTs.

We have in this chapter looked at what homeopathy is and its' prevalence of use. Following a brief overview of the overall evidence base for homeopathy in the research literature, a systematic review of the research literature assessing homeopathy in depression has been presented. The following chapter will present the methods used for the research project presented in this thesis.

4. Methods

This chapter describes the methods used for a pragmatic RCT, a qualitative interview study and a mixed methods approach used to assess treatment provided by homeopaths for patients with self-reported unipolar depression.

1.1 Aims of this thesis

The primary aim of this thesis is to assess the effectiveness of offering treatment by homeopaths for patients with self-reported depression. The secondary aims are to assess the acceptability and the safety of treatment provided by homeopaths and learn about patients' experiences with this treatment.

The aims of the research project are:

I. to evaluate if treatment provided by homeopaths, as an adjunct to usual care, is acceptable, safe and effective for patients suffering from self-reported unipolar depression; and
II. to explore what patients with self-reported unipolar depression experience during and after treatment provided by homeopaths as an adjunct to usual care.

4.1 Randomised controlled trial (RCT) using the "cohort multiple" RCT design

The methods for a pragmatic RCT are described in this section, including a description of the "cohort multiple" RCT design; the cohort (the Yorkshire Health Study); screening and data collection procedures; inclusion and exclusion criteria; a sample size calculation; random selection procedures; recruitment procedures; the intervention and the setting; data that is collected; reporting of baseline data and data assessing the acceptability, the safety and the effectiveness of the treatment provided by homeopaths for patients with self-reported unipolar depression, including statistical analyses and methods for dealing with missing data.

4.1.1 Pragmatic randomised controlled trial (RCT)

The aims of this research project include the testing of the clinical effectiveness of treatment provided by homeopaths in addition to usual care compared to usual care alone for patients suffering from self-reported depression. The RCT method is considered the "gold standard" for assessing the effectiveness of interventions in health research (Torgerson & Torgerson 2008). Random allocation of patients into trial arms reduces the problem of selection bias. It helps to control for variables that could otherwise be known and unknown confounding factors. Due to randomisation these factors are equally distributed between treatment groups and therefore influence the results of patients to a similar extent in the two arms of the trial. Patients' state of health changes over time and regression to the mean effects affect measured outcomes. Such changes are likely to be significant in depression, due to its episodic nature, but the magnitude of these changes can due to random allocation be assumed to be equally present in both trial groups. A pragmatic RCT can therefore help to answer the question of the effectiveness of the intervention.

The vast majority of published health research trials are explanatory (Treweek & Zwarenstein 2009, Zwarenstein & Treweek 2009). This is also true for research in homeopathy in general and for homeopathy in depression in particular. Double-blinded placebo-controlled trials are explanatory. They are best suited to test the efficacy of a particular intervention such as an antidepressant drug. These trials usually involve more restrictive inclusion and exclusion criteria, stricter criteria for application of the intervention and comparator, more controlled settings and more often short-term outcomes. Pragmatic trials use wider inclusion criteria, fewer and less restrictive exclusion criteria, they are more often carried out in normal practice, treatments can be applied in a more flexible way, and outcomes are often more relevant to patients. In brief, explanatory trials test the efficacy of an intervention under more ideal conditions, whereas pragmatic trials test the effectiveness of whole treatment packages in ways that are more comparable to everyday practice. This often makes pragmatic trials more relevant to patients, practitioners and decision makers (Treweek & Zwarenstein 2009). The pragmatic trial presented in this thesis will hopefully contribute to the overall evidence needed for decision-making processes.

4.1.2 The "cohort multiple" RCT design

This pragmatic trial was planned to be carried out using the "cohort multiple" RCT design (Relton et al. 2010). This method makes it possible to carry out a number of trials within an existing large observational cohort of patients.

The use of the a cohort would give access to patients who had already provided data, who had consented for their data to be used to look at benefits of treatments and who had consented to be contacted again. The use of the cmRCT design was therefore likely to shorten the recruitment period and to reach recruitment targets.

The use of the cmRCT design enables data collection from patients without having to inform them that they have been randomly selected to the control group. Only patients who receive the offer of treatment are provided information about the trial and are asked for consent to participate.

Patients, clinicians and NHS Research Ethics Committees have found the cmRCT design to be acceptable (Relton et al. 2010), and it is being applied in trials within and outside the UK (Ahmed et al. 2014, Kwakkenbos et al. 2013, Relton et al. 2011, Sepanlou et al. 2013).

4.1.3 The Yorkshire Health Study (YHS)

This trial is embedded in and recruits patients from the Yorkshire Health Study (YHS) (herein after referred to as "the cohort"), formerly known as the South Yorkshire Cohort (SYC). The cohort was first established in 2009 and included patients recruited through 43 GPs in South Yorkshire, in the boroughs of Barnsley, Doncaster, Rotherham and the city of Sheffield and the surrounding areas (Green et al. 2014). A total of 27,806 (17.7%) of 156,866 health questionnaires sent to patients recruited by GPs were returned, with 22,179 (79.8%) giving consent to being contacted again. Compared to the overall South Yorkshire population, cohort participants were on average slightly older, more were female (56.2% in the cohort, 51.7% in the general population) and of White ethnicity (94.1% versus 90.5%), and less likely to belong to the two lowest quintiles of deprivation (43.4% versus 57.1%). Cohort patients provided information on long-standing conditions, including long-standing depression, and degrees of anxiety or depression (Euro-QoL-5D). The fact that Yorkshire

Health Study participants consented to be contacted again and that their basic data had been collected, was expected to facilitate the screening process for this trial.

4.1.4 Screening and data collection

Patients included in the cohort who had previously returned a cohort Health Questionnaire providing basic general and health information and who self-reported long-standing depression were sent a letter (Appendix 5: Letter to patients for screening and baseline data collection) asking patients to provide additional health information (but with no mention of the homeopathy treatment arm), together with a baseline Mood and Health Questionnaire (Appendix 6: Mood and Health Questionnaire). If the response rate was insufficient, questionnaires were to be sent to all cohort patients who previously indicated they suffered from moderate or severe anxiety or depression (on EQ-5D), or to the entire cohort. All patients who fulfilled the inclusion criteria received follow-up questionnaires 6 months later (Appendix 7: Mood and Health Questionnaire – follow-up). Pre-paid postage response envelopes were used.

The screening and baseline Mood and Health Questionnaire included (full questionnaire attached):

- the Patient Health Questionnaire (PHQ-9);
- the Generalized Anxiety Disorder scale (GAD-7);
- the EuroQoL (EQ-5D);

  and questions about:
- long-standing conditions (tiredness/fatigue, insomnia, anxiety/nerves, depression, other) together with a question about when each long-standing condition first started and when the current episode started;
- current medication and past use of antidepressants;
- use of healthcare services and other treatment;
- current pregnancy and children under the age of 18;
- height and weight;
- employment status;
- ill health resulting in absence from work, household and leisure activities;
- alcohol consumption;

- involvement in other health studies;
- consent to be contacted again

An extended version of the screening and baseline Mood and Health Questionnaire did in addition include the Measure Yourself Medical Outcome Profile (MYMOP2) and a life satisfaction score. The regular and the extended version were tested on the first 200 patients (100 for each version). A decision was made one month after testing the first 200 questionnaires to determine whether the shorter or longer version was used.

The 6 month Mood and Health Questionnaires included the same questions as the screening and baseline version, with the following changes:

- Added: In the long-standing conditions section: pain, memory problems, diabetes, breathing problems, high blood pressure, heart disease, osteoarthritis, stroke and cancer;
- Omitted: The question of when conditions and episodes of conditions first started; past use of antidepressants, current pregnancy and children under the age of 18, height and weight, and involvement in other health studies.

Non-responders were sent reminders by post, and in case of no response, telephoned or emailed and asked if they were willing to complete the questionnaire over telephone with an interviewer. Further description of the outcome measures follows here.

The Patient Health Questionnaire (PHQ-9)

The Patient Health Questionnaire (PHQ-9) poses questions to determine the frequency of symptoms that may be related to depression. It is not intended to replace diagnostic depression tools such as the structured clinical interview for DSM disorders (SCID). However, it is based on DSM diagnostic criteria for major depressive disorder (Kroenke et al. 2001) and its characteristics have been tested in various studies and results suggest that it is a useful tool for screening of depressed patients (Kroenke et al. 2010). The nine questions posed in PHQ-9 correspond closely to the nine key symptoms used to diagnose depression according to the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-V) (APA 2013) (table 1). PHQ-9 is commonly used both in routine clinical practice as well as in depression research. Another important reason for using the PHQ-9

questionnaire for screening, baseline data collection and as the primary outcome measure, was its brevity. Outcome measures commonly used in research such as the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI) include 17 and 21 questions respectively. It was hoped that the use of PHQ-9 with only 9 questions would reduce the burden put on patients who are depressed and who therefore may lack energy, feel indifferent and be easily overburdened by longer questionnaires. Moreover, other researchers have found PHQ-9 to be comparable to outcome measures such as HDRS and BDI, with high validity, reliability, sensitivity and specificity, sensitivity to change, for patients with various comorbidities (Kroenke et al. 2010, Löwe et al. 2004a, 2004b, 2006).

The Generalised Anxiety Disorder (GAD-7)

The Generalized Anxiety Disorder scale (GAD-7) poses seven questions to assess the frequency of anxiety symptoms. Although it was primarily developed in order to identify patients suffering from generalized anxiety disorder (Spitzer et al. 2006), it has been found to be useful in assessing anxiety in heterogeneous samples of patients (Beard & Björgvinsson 2014).

Measure Yourself Medical Outcome Profile (MYMOP2)

The Measure Yourself Medical Outcome Profile (MYMOP2) was developed in order to assess outcomes in patients using complementary and alternative medicine (CAM) treatment (Paterson 1996). It may be used in clinical practice as well as in research. The questionnaire is used to assess patients' two "most bothersome" symptoms, their level of activity and general feeling of wellbeing. MYMOP2 is normally not used as a postal questionnaire, but is completed by patients sometime during their first consultation with a CAM practitioner. It was therefore only going to be included in this trial if responses to a sample of 100 patients were to suggest that patients understand how the questionnaire should be completed and if would not contribute to reduced response rates.

4.1.5 Inclusion and exclusion criteria

Patients included in the trial had to:

- have self-reported depression indicated by a minimum PHQ-9 score of 10 with a minimum of two symptoms scoring 2 points, with at least 2 points for either question 1 (little interest or pleasure in doing things) or question 2 (feeling down, depressed, or hopeless);
- be in the age from 18 to 85 years;
- be able to speak and read English; and
- have given informed consent.

Patients were excluded if they:

- had PHQ-9 scores below 10 or less than 2 symptoms scoring 2 points, or neither question 1 nor question 2 scoring 2 points;
- had a current or past psychiatric diagnosis (other than depression) including bipolar disorder, Alzheimer's disease, organic brain damage, schizophrenia, schizoaffective disorders, other psychotic disorders, or antisocial personality disorder;
- had received homeopathic treatment over the past 3 months;
- were currently involved in another health research project; and
- were unable to read or understand study questionnaires and accompanying information due to reduced intellectual capacity or illiteracy.

4.1.6 Sample size calculation

The primary outcome measure in this trial was the PHQ-9 score at 6 months post-randomisation. The level of significance (alpha error) was set to 0.05 and the power to 80 %, as considered reasonable in clinical research (Whitley & Ball 2002). No pragmatic RCT has previously been carried out to assess the effectiveness of individualised treatment provided by homeopaths for patients suffering from self-reported depression. There was therefore no homeopathy research on which to base the expected effect size. It has been suggested that in order to consider any treatment modality worthwhile recommending, the effect size (*d*) should preferably be at least medium (Cohen 1988). It might however not be reasonable to expect a medium effect size of a treatment modality which is given in

addition to usual care, and even a small added effect size might be of importance to patients when added to the effect of other treatment. Moreover, the way in which effect sizes are interpreted varies somewhat between researchers. The effect size used for the sample size calculation for this study was set to 0.35, which could be considered to be in the range from small to medium. It was estimated that 40 % of cohort participants would return screening questionnaires. In addition, the expected drop-out rate was set to 40 %. This gave a final sample size of 485, with 162 in the "Offer" (for homeopathy) group and 323 in the "No offer" (usual care) group (see calculations below). A "rolling recruitment" procedure was applied.

The sample size calculation can be described with the following three formulas, in line with Whitley & Ball (2002):

a) Sample size calculation per arm for equally sized trial arms

$[2 / (d)^2]$ x [c p,power value] = $[2 / (0.35)^2]$ x [7.9] = 129

N (two groups) = 129 x 2 = **258 patients**

Where: c p,power value = 7.9 (for power 80% and alpha 0.05). Effect size (d) = 0.35.

b) Adjusted sample size given unequal randomisation

Unequal randomisation (ratio 1:2 for Offer group:No offer group)

$N' = [N(1+k)^2] / 4k = [258(1+2)^2] / 4x2$ = **290 patients**

Where: N' = total sample size using unequal randomisation;

N = total sample size for equal randomisation;

k = group ratio (for 1:2 randomisation k=2).

c) Sample size taking account of attrition rate 40 %

40 % attrition rate gives 60 % remaining in the trial:

N' = 290 * 100 / 60 = **484 patients**

Offer group: 1 * (484/3) = **162 patients**. No offer group: 2 * (484/3) = **323 patients**.

Final sample size: **N' = 484**, **Offer group n = 162**, **No offer group n = 323**.

In conclusion, the calculated sample size (N) was 484, with 162 patients in the "Offer" group and 323 in the "No offer" group. As the trial used rolling recruitment, the final sample size was likely to differ from the pre-calculated sample size.

4.1.7 Random selection of patients included in the trial

One third of the eligible trial population were randomly selected to receive the offer of treatment provided by a homeopath as an adjunct to usual care. Random selection was carried out among those who responded to the screening questionnaire and who fulfilled the inclusion criteria, and was carried out by a statistician not otherwise involved in the project. Unequal randomisation was applied, with only one in three patients randomly selected to the "Offer" group (ratio 1:2 for Offer group:No offer group). Using a 1:2 ratio increased the final sample size, but reduced the number of patients included in the "Offer" group, thereby reducing expenses for the provided intervention and therefore reducing the overall costs of the trial.

4.1.8 Recruitment of patients offered the intervention

Patients fulfilling the inclusion criteria and randomly selected to receive treatment by a homeopath were sent a letter with the treatment offer (Appendix 8: Offer group – Treatment offer letter), a patient information sheet (Appendix 9: Offer group – Participant Information Sheet) followed by a phone call from the research team after 48 hours at the earliest. Patients were asked if they had received the letter with the offer and whether they had any questions. Those patients who were interested in participating were asked to complete and return the consent form (Appendix 10: Consent form). Patients not reached by telephone were sent an email. "No offer" group participants (control group) were not informed that they had not been selected for treatment, but were sent the same follow-up questionnaires at the same time intervals as "Offer" group participants. All documentation had been approved by the NHS Research Ethics Committee.

4.1.9 The intervention and the setting

The intervention, treatment provided by a homeopath, was offered for a maximum period of 9 months. It consisted of any number and length of consultations as deemed necessary by the homeopaths. Homeopaths were free to practise as they would normally do and could prescribe homeopathic medicines and provide any additional advice as deemed relevant for each individual patient. The offer of treatment was provided by seven homeopaths of which two practise in Barnsley, one in Doncaster, three in Rotherham and four in Sheffield (one Barnsley and two Sheffield practitioners also offer treatment in Rotherham). All practitioners were members of the Society of Homeopaths (http://www.homeopathy-soh.org), the largest professional registering body for homeopaths in the UK.

Treatment was delivered at a range of locations in South Yorkshire including:

- **Barnsley**: *Western House Consulting Rooms*, a clinic normally used by private medical and surgical consultants, as well as various complementary therapy practitioners (www.westernhouseconsultingrooms.co.uk);
- **Doncaster**: *Chapman Physiotherapy*, a practice specialising in physiotherapy, but also offering a range of complementary therapies (www.chapmanphysiotherapy.com);
- **Rotherham**: *Clifton Medical Centre*, a medical centre which hosts several GPs, nurses and other health team members (www.cliftonmedicalcentre.co.uk);
- **Sheffield**: *The Dovercourt Surgery*, a medical centre including GPs, nurses and a Primary Health Care Team (http://www.dovercourtsurgery.co.uk); and *Wellforce Integrated Medicine Service*, a complementary medicine centre (www.wellforce.co.uk)

Usual care for both the Offer and the No offer group consisted of any treatment patients were receiving at that time, such as medication and consultations provided by patients' GPs, psychiatrists, psychologists or other healthcare workers.

4.1.10 Practitioner and homeopathy treatment data

Data was collected from the homeopaths included in the trial in order to determine their gender, age, education, clinical experience, organisational affiliation and homeopathy approach. Homeopathy treatment data includes the length and number of consultations for

treated patients, prescriptions made, homeopaths' confidence in their prescriptions and expectations of improvement in patients' symptoms, and any other advice given to patients.

4.1.11 Reporting of baseline data

Baseline demographics and patient reported outcome measure (PROM) data were assessed for comparability between the groups. The following baseline data were reported for each of the two trial arms:

A. **Demographics**:

- Gender (categorical)
- Age (continuous)
- Ethnic group (categorical)
- Having children up to 2 years of age (yes/no) (categorical)
- Being pregnant (yes/no) (categorical)
- Employment status (yes/no) (categorical)
- City/region (categorical)
- Deprivation score (quintile) (categorical)

B. **Health measures**:

- PHQ-9 score (continuous)
- PHQ-9 depression severity groups (moderate 10-14, moderately severe 15-19, severe 20-27) (categorical)
- GAD-7 score (continuous)
- GAD-7 anxiety severity groups (minimal 0-4, mild 5-9, moderate 10-14, severe 15-21) (categorical)
- BMI score (continuous)
- BMI category (underweight < 18.50, normal 18.50-24.99, overweight 25.00-29.99, moderately obese 30.00-34.99, severely obese 35.00-39.99, very severely obese from 40.00) (categorical) (WHO 1995)
- Alcohol consumption (number of days & units) (continuous)

- Long-standing condition (tired/fatigue, insomnia, anxiety/nerves, depression, other) (yes/no) (categorical)
- Number of long-standing conditions (continuous)
- Length of time since onset of depression & current episode of depression (continuous)

C. **Medication and other treatment use**:

- Antidepressant use (current) (yes/no) (categorical)
- Antidepressant use (past) (yes/no) (categorical)
- Other medication (number of patients using medication and number of drugs per patient) (categorical and continuous)

Baseline characteristics of all included patients were compared to those with outcomes for analysis at 6 months, as suggested by Walters (2009). Moreover, a multiple linear regression model was conducted, using baseline PHQ-9 values as the outcome, together with: treatment group ("Offer" group and "No offer" group), response status (patients with and without PHQ-9 scores for 6 month assessment) and treatment group x response status interaction terms as explanatory variables (Walters 2009):

$PHQ\text{-}9_{Baseline} = b_0 + b_{1(Group)} + b_{2(Responder)} + b_{3(Interaction)}$

With: *b_0 = constant; b_1Group = "Offer" group and "No offer" group;*
b_2Responder = Patients with and patients without PHQ-9 scores for 6 month assessment;
b_3Interaction = Treatment group ("Offer group"=1, "No offer" group=0) x response status interaction (Patients with 6 month PHQ-9 scores=1, Patients without 6 month PHQ-9 scores=0)

4.1.12 The acceptability of treatment provided by homeopaths for depressed patients

The acceptability of the offer of treatment provided by a homeopath was assessed by considering the proportion of patients accepting the offer and having at least one consultation with a homeopath. Identified reasons for non-acceptance of the offer were presented.

4.1.13 The safety of treatment provided by homeopaths for depressed patients

The safety of treatment provided by homeopaths for depressed patients was assessed by considering the number and nature of reports submitted by homeopaths, patients and their clinicians, or through information obtained during qualitative interviews. Guidelines for assessing, reporting and dealing with adverse events and potential risk were developed specifically for this research project. The adverse events guidelines (Appendix 11: Adverse Events Assessment Guidelines for the DEPSY project) are mainly based on the Common Terminology Criteria for Adverse Events (CTCAE) (NIH/NCI 2010) and the Standard Operating Procedure developed by the Clinical Trials Research Unit (CTRU) at the University of Sheffield (2012). The risk guidelines (Appendix 12: How to identify and deal with clinical risk issues: Guidelines for homeopaths providing treatment in the DEPSY project) were mainly based on the clinical risk protocol developed by Sheffield Mind (2011, undated), supplemented by the guidelines for management of depression developed by the National Collaborating Centre for Mental Health (NCCMH 2004). The homeopaths and researchers involved in the research project all had training to familiarise themselves with these guidelines.

4.1.14 The effectiveness of treatment provided by homeopaths for depressed patients

Effectiveness data included assessment of scores for PHQ-9 and GAD-7 at 6 months as described in the following sections. An intention-to-treat (ITT) analysis was the primary method of analysing outcomes in the trial, as it is the most appropriate analytical approach for testing the offer of treatment.

The analysis was to include all patients with the exception of those who would be excluded due to any of the predefined exclusion reasons (section 4.1.5: Inclusion and exclusion criteria). For the ITT-analysis patients remained in the group they were randomly allocated to, irrespective of whether "Offer" group patients had received treatment by a homeopath or not, whether "No offer" group patients sought such treatment by their own initiative, and whether patients had completed all questions in any of the Mood and Health Questionnaires (at baseline and 6 months).

Although the ITT-analysis strategy is the best approach to test the offer of treatment, it includes non-compliers and does therefore not assess the effect in patients who do take up the offer and receive the treatment (Hewitt et al. 2006). A low uptake of the offer of treatment in this pragmatic trial, or a high attrition rate would underestimate any potentially existing treatment effects. A per-protocol analysis, often used as a secondary (and by some primary) analysis will often tend to produce more "inflated" results and has a higher risk of bias, particularly in pragmatic trials. A "way in between" these two approaches is the use of the complier average causal effect (CACE) analysis, which was to be carried out as part of the analyses for this trial. It assesses the causal effect of the intervention for those patients who receive the treatment offered, as intended according to group allocation (Hewitt et al. 2006).

Analysis of primary outcome (PHQ-9 at 6 months)

As this was a pragmatic randomised trial, with a usual (control) treatment arm, data was reported and presented according to the revised CONSORT statement (Schulz et al. 2010). All statistical exploratory tests were two-tailed with alpha = 0.05.

The aim of the analysis was to establish firstly whether there were benefits from the offer of a homeopathic intervention, i.e. comparing an "Offer group" with a "No offer" control group. The choice of 6 months as time for assessing the main outcome was made in consultation with the homeopaths providing the intervention. The practitioners suggested that patients should experience improvements in their mood at least after 6 months of treatment. The primary analysis used general linear model (GLM) with baseline PHQ-9 scores as a covariate. Secondary analyses would include GLM with all relevant baseline covariates (see below). Moreover, since the homeopathic intervention is a therapist-based

intervention, there could be clustering or correlation of the participants' outcomes and treatment offered by a particular homeopath. Therefore, to make allowance for this, the analyses compared mean PHQ-9 scores at six months, post-randomisation, between the intervention group and control group using a marginal general linear model (GLM), with robust standard errors, and an exchangeable correlation (Walters 2010). The marginal model used generalised estimating equations (GEE) to estimate the regression coefficients. Patients in the control group were treated as one cluster in the analysis. The exchangeable correlation assumed that participant outcomes within each cluster (homeopath group) would have the same correlation. A 95% confidence interval (CI) for the treatment group coefficient, the difference in PHQ-9 scores between the intervention and control group, was also calculated. The baseline covariates considered to be most important included the following:

A. PHQ-9 score
B. Use of antidepressant drugs (yes/no)
C. Number of long-standing conditions (i. 0 to 3 LSC, compared to ii. 4 or more LSC)
D. GAD-7 score

However, all baseline covariates were considered for inclusion, following the assessment using a hierarchical model.

For the primary outcome, the PHQ-9 score at six months post-randomisation, missing data were imputed through a variety of methods, including Last Observation Carried Forward (LOCF), Regression Imputation (RI) and Multiple Imputation (MI). MI was selected as the primary method used for replacing missing data, as it was expected to give a somewhat more conservative result than using no imputation for missing data. In MI, missing values are replaced several times and by a number of plausible values and the use of several imputed values represents the uncertainty that missing values involve (Rubin 1987). Under the assumption of data missing completely at random (MCAR) and missing at random (MAR), MI has been found to have smaller risk of bias compared to for example LOCF (e.g. Zhu 2014). (For further information on imputation methods, see separate sections below.)

Effect size

The effect size used for calculation of the sample size in this trial was set to 0.35 (small to medium) (Cohen 1988). For calculating the results of the trial, the following formula was used to estimate the effect size: ES = M1-M2/SD1 (ES=effect size, M1=mean PHQ-9 score at time 1, M2=mean PHQ-9 score at time 2, SD1=standard deviation for the PHQ-9 score at time 1) (Kazis et al. 1989). Effect sizes for the two groups ("Offer" and "No offer" group) was then compared to determine if there was at least a 0.35 difference in favour of the "Offer" group. A minimum between-group difference of 0.35 would suggest a clinically significant result.

Analysis of secondary outcome

The secondary outcome, the GAD-7 score at 6 months, was used for between-group comparison, as for the primary outcome measure. A 95% confidence interval (CI) for the mean difference was calculated.

Interaction analysis

Interaction analyses to consider combined effects of baseline covariates on the outcome measures (Field 2009) were carried out using the following baseline covariates:

A. PHQ-9 score
B. Use of antidepressant drugs (yes/no)
C. Number of long-standing conditions (i. 0 to 3 LSC, compared to ii. 4 or more LSC)
D. GAD-7 score
E. Depression onset (number of years/months ago)
F. Employment status (yes/no)
G. BMI score
H. Alcohol consumption (units per week)

Separate models were used with an interaction term for each model, in the following way:

$$PHQ\text{-}9_{6\ months} = Group_{BL} + PHQ\text{-}9_{BL} + Interaction_{BL}\ (Group_{BL} \times PHQ\text{-}9_{BL})$$

Where: $PHQ\text{-}9_{6\ months}$ = PHQ-9 score at 6 months; $Group_{BL}$ = "Offer" group and "No offer" group at baseline; $PHQ\text{-}9_{BL}$= PHQ-9 scores at baseline; $Interaction_{BL}$ = Group at baseline ("Offer group"=1, "No offer" group=0) x PHQ-9 scores at baseline

Similar models were developed for each of the listed baseline covariates.

The following covariates were considered, but not included: Depression episode onset, gender, age, and deprivation score (according to geographical area).

Missing data

Missing data is not uncommon in longitudinal clinical trials. An important question is whether there is a pattern suggesting that data is missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR) (Rubin 1976). Testing was carried out in order to identify any possible baseline differences between adheres and non-adheres (Peduzzi et al. 2002, Wright & Sim 2003). A posteriori tests were performed if any differences were identified.

It is unlikely that "No offer" group patients in this trial would use the "Offer" treatment (homeopathy), as they were not informed about the offer treatment. It was however probable that a significant number of "Offer" group patients would not accept the offer, thereby only using "treatment as usual". Comparison of "non-adherers" was therefore only relevant for the "Offer" group. The trial was not going to include a specified homeopathy treatment program. It was entirely up to each individual practitioner to determine, in each individual case, the length of a single consultation and to recommend a single or several consultations, as well as the use of a single or several homeopathic medicines and to recommend any additional treatment modalities. Treatment adherence was here defined as having had at least one consultation with a homeopath.

Missing primary outcome data were imputed using the following methods: Last Observation Carried Forward (LOCF), Regression Imputation, and Multiple Imputation. As recommended by Liu et al. (2006), in order to preserve the ITT population, data

continued to be collected for patients who did not accept the offer of treatment or who accepted the offer, but later withdrew from treatment.

Last observation carried forward (LOFC)

Baseline PHQ-9 data were used to input any missing six month outcome data.

Regression imputation

A multiple regression model was to be used to impute missing scores using baseline covariates including at least:

A. PHQ-9 score
B. Use of antidepressant drugs (yes/no)
C. Number of long-standing conditions (i. 0 to 3 LSC, compared to ii. 4 or more LSC)
D. GAD-7 score

A decision on additional covariates to include was made depending on the available data and likelihood of influence of each covariate, and after considering the risk of multicollinearity between covariates. The following additional baseline covariates were considered as they have been found in other research to be correlated to depression outcomes:

1. Onset of depression (number of years/months ago)
2. Employment status (yes/no)
3. BMI score
4. Alcohol consumption (units per week)
5. Deprivation quintile (IMD score range: **1**[least deprived area]: ≤8.49, **2**: 8.5-13.79, **3**: 13.8-21.35, **4**: 21.36-34.17, **5** [most deprived area]: ≥34.18)
6. Gender
7. Age

Multiple imputation

A Multiple Imputation analysis was carried out, using the same covariates as in the Regression Imputation.

Complier Average Causal Effect (CACE) analysis

It is not unreasonable to assume that the uptake of the offer of treatment in this trial would be low, as patients fulfilling the inclusion criteria and randomly selected to the "Offer" group were not informed about the intervention prior to random selection. In addition, attrition rate could be high. The ITT-analysis includes non-compliers and is therefore likely to underestimate any potentially existing treatment effect. A per-protocol analysis might result in "inflated" results and has a higher risk of bias, particularly in pragmatic trials. A complier average causal effect (CACE) analysis was therefore carried out. CACE analysis assesses the causal effect of the intervention for those patients who receive treatment, as intended according to group allocation (Hewitt et al. 2006). It is carried out with two assumptions:

A. The probability of non-compliers is equal in the two groups. This is a reasonable assumption as patients were randomly allocated to the two trial groups.
B. Being offered treatment would not in itself affect the outcome.

Compliers' mean PHQ-9 scores at 6 months were compared to the mean PHQ-9 scores at 6 months for those participants in the "No offer" group who would have complied had they received the offer. Compliers were those patients who had a least one consultation with a homeopath. It was, as this is a RCT, reasonable to assume that the proportion of patients in the "No offer" group who would have complied had they received the offer is similar to the proportion of compliers in the "Offer" group. The proportion of non-compliers in the two groups should also be comparable, as would their mean PHQ-9 scores. The following was known:

- The number of "No offer" group patients overall and their mean PHQ-9 scores;
- The number of "No offer" group patients who would not have complied and their mean PHQ-9 scores; and
- The number of "No offer" group patients who would have complied.

Based on this information, the mean PHQ-9 scores can be calculated for those "No offer" group patients who would have complied had they received the offer of treatment (Nicholl 2012). As the outcome measure was continuous, each part of the equation had to involve multiplication of the number of participants with the mean PHQ-9 score at 6 months. The calculation can be expressed using the following formula:

$(N_{noc} \times \bar{x}_{PHQ\text{-}9noc}) + (N_{nonc} \times \bar{x}_{PHQ\text{-}9nonc}) = (N_{no} \times \bar{x}_{PHQ\text{-}9no})$
Which is the same as: $(N_{noc} \times \bar{x}_{PHQ\text{-}9noc}) = (N_{no} \times \bar{x}_{PHQ\text{-}9no}) - (N_{nonc} \times \bar{x}_{PHQ\text{-}9nonc})$
Which is the same as: $\bar{x}_{PHQ\text{-}9noc} = [(N_{no} \times \bar{x}_{PHQ\text{-}9no}) - (N_{nonc} \times \bar{x}_{PHQ\text{-}9nonc})] / N_{noc}$

Where: N = number of participants; $\bar{x}_{PHQ\text{-}9noc}$ *= mean PHQ-9 score*
no = "No offer" group; noc = "No offer" group complier;
nonc = "No offer" group non-complier

Following this, the mean PHQ-9 scores for compliers in the "Offer" and "No offer" group can be compared and the difference in effect size between the "Offer" and "No offer" group can be calculated.

4.2 Patients' experiences: A qualitative semi-structured interview study

No previously published qualitative studies reporting on depressed patients' experiences with treatment provided by homeopaths were identified through the systematic review. The qualitative study presented in this thesis was to explore patients' experiences with treatment provided by homeopaths as an adjunct to usual care for self-reported unipolar depression (experiences can be positive and negative, short and long term).

The methods for this qualitative semi-structured interview study and described in this section include the reasoning for using qualitative research; a presentation of thematic analysis; the selection method, selection criteria and sample size; the recruitment procedures; the time and venue for planned interviews; the various stages of the qualitative research project; and the measures put into place in order to strengthen the trustworthiness of the results of the qualitative interview study.

4.2.1 Why use qualitative research to learn from patients' experiences?

Where research tools such as questionnaire surveys may be helpful in collecting data that can be quantified, qualitative methods may be helpful in order to gain more in-depth knowledge about people's experiences and hereunder their thoughts, understandings and views (Fossey et al. 2002, Kvale 2007, Mason 2002). We experience the world affectively and depression has a strong affective component. Qualitative methods could therefore be better suited than quantitative methods to learn more in depth about depressed patients' experiences with treatment provided by homeopaths. The terms "patient", "interviewee", "researched" and "participant" are used intermittently in the following, and all refer to the patients who were interviewed as part of this research project.

Qualitative research is dependent on the researcher, the researched and the context (Kvale 2007, Mason 2002, Ritchie & Lewis 2003). The degree to which qualitative research interviews contribute to a detailed, rich and nuanced understanding of people's experiences, views and thoughts depends on the interaction between the researcher and the researched; their interpretation of each other's questions and responses; as well as the context within which it takes place (Kvale 2007, Mason 2002). It is an inductive process where people can give a rich insight so we may better understand what is happening to them and how they themselves understand this (Kvale 2007, Silverman 2000), in this particular context this would be how depressed patients experienced and understood treatment provided by homeopaths.

The results of qualitative research can contribute to existing knowledge within a particular area of interest and might also be transferable to other contexts (Lincoln & Guba 1985, Rodwell & Byers 1997). Potential transferability of results will be addressed in the results chapter.

Measures were put into place in order to strengthen the trustworthiness of the results. Readers should be able to follow the various stages of the research process and the researcher's line of reasoning. To enable this, the used research methods and results were described as clearly as possible. Further details on how to strengthen trustworthiness of the results are addressed in the following sub-sections, in particular in section 4.2.6 (Trustworthiness of the results from the qualitative interview study).

4.2.2 Using thematic analysis to learn from patients' experiences

Inductive thematic analysis was used as the qualitative research method to learn about depressed patients' experiences with treatment provided by homeopaths. The protocol for the project suggested that framework analysis would be used to analyse results of the qualitative interview study. However, as no previous research assessing depressed patients' experiences with treatment provided by homeopaths was identified in the systematic review, it was decided that it was more appropriate to use thematic analysis. Framework analysis involves the use of a pre-determined framework for the analysis, which in this case could not be developed, due to the lack of similar research in the same field.

Using an inductive approach helps themes to be more strongly linked to patients' statements, instead of trying to fit data to pre-conceptions or existing frameworks (Braun & Clarke 2006) allowing it to be driven by the data to a greater extent than theoretical thematic analysis. Thematic analysis may be understood as a method used to identify, analyse and report themes within data (Braun & Clarke 2006, 2013). The word "identify" may give the impression that the research themes are to be found "out there" and that the researcher's task is to identify them. However, the researcher contributes more actively in the research process, through interaction with patients and interpretation of what patients communicate. It was therefore more appropriate to state that research themes are "developed" through the research process, both during the interviews and in the following analytical stage. Themes would be emergent through the process where the researcher codes data (Williams, in: Given 2008). Patients' statements would be processed in the mind of the researcher, who would then develop themes based on his understanding of patients' statements. Although some ideas might be more explicit, more easily "identified" in patient interviews, and others would be more implicit, thereby requiring a greater degree of interpretation (Guest et al. 2012), all would in reality be processed through the mind of the researcher and thereby developed by the researcher. Having said this, the researcher attempts, as much as possible, to stick to patients' descriptions of their experiences. By using an inductive approach, he develops codes and theory based on patients' statements during interviews, as opposed to applying a "top-down" approach this is based on pre-existing theories and concepts (Wengraf 2001). The analytical work was carried out at two levels, firstly by identifying and coding statements made by individual patients, and then by analysing statements across interviews.

The element of developing themes is common for various qualitative methods (Holloway & Todres 2003). The intention was that these themes would give meaning to and describe what depressed patients said about their experiences with and thoughts about the treatment they had received from homeopaths. There is not one commonly agreed understanding or definition of thematic analysis as a method, but there are some typical characteristics. Firstly, it is inductive. Patients' responses are used as the primary source of information. No theoretical thematic analysis was carried out prior to starting the first interviews. Interviews were used to develop themes and no pre-conceived understanding or views of treatment provided by homeopaths for depressed patients was required. Secondly, thematic analysis is considered to be theoretically flexible, so it may be used by researchers who may or may not adhere to particular ontological and epistemological views (Braun & Clarke 2006). It therefore also fits with the pragmatic approach chosen for this project. Further characteristics of the method used are presented in the following sections.

4.2.3 Inclusion criteria, purposeful selection of patients and sample size

As the aim of the qualitative study was to explore depressed patients' experiences with treatment provided by homeopaths as an adjunct to usual care, only patients who had received treatment by a homeopath were included. Moreover, patients were only those who were taking or who had taken antidepressants or used other forms of treatment for their depression in the past, in order to enable comparison of experiences with these forms of treatment to experiences with treatment provided by homeopaths.

Maximum variation sampling (Patton 1990) was used as this approach can help to capture a variety of experiences within a given group of interviewees. It is a form of purposive sampling, which suggests that the researcher selects participants who are likely to provide rich information that will help answer the research question. In maximum variation sampling interviewees are selected due to having some common characteristics, but within the sample there should also be as much variation in participants' characteristics (e.g. gender, age, intensity of depression) as possible in order to capture a wider variety of experiences.

This is contrasted with for example homogeneous sampling, where interviews with a group of participants with more identical characteristics could help to learn more about a more homogeneous group of people. It is also different to extreme case sampling, where interviews provide knowledge about experiences that deviate to a greater extent from a more homogeneous sample. This could for example have been only those patients who did particularly well or who got much worse following treatment provided by a homeopath, in order to learn from successes and failures. In maximum variation sampling such experiences are included, as it involves a variety of participants, but it is not an aim in itself. This means that in this project there was a risk that we might not identify the more "extreme" cases. It is possible, as all patients treated by homeopaths would not be interviewed, that we might miss out on some experiences that could have contributed significantly to the results. However, reducing the number of interviewees contributes to reducing the resources needed to carry out the research. Maximum variation sampling considers issues from different angles, whilst identifying themes common across the sample. The results therefore provide more nuanced variation contributing to a broader spectrum of experiences, as well as identifying common patterns within the group of interviewed patients.

For these reasons, patients of both genders, different age groups, treated by different homeopaths, living in different cities and boroughs, and suffering from different degrees of self-reported depression (moderate, moderately severe and severe depression according to their PHQ-9 scores) were invited to participate and a variety of patients with different baseline characteristics was included. Their socio-demographic information was to be presented. The use of depression categories as part of the selection process can be referred to as criterion sampling (Sandelowski 2000). Interviews were only carried out with patients who had given their informed consent to participate.

Theoretical saturation was used to determine the number of patients interviewed, with the maximum number set to 30 due to financial and time constraints. The concept of theoretical saturation has been subject to considerable debate and is often not clearly defined (Guest et al. 2006). It suggests that saturation has been reached when no new information is provided through new interviews (Lincoln & Guba 1985). Theoretical saturation is considered to be an ideal, but in principle it requires unlimited time and resources (Patton 1990). The reason for this is that it is impossible to know with certainty

that no new information contributing to development of new themes could have been identified had one or several more interviews been carried out. Therefore, the concept of theoretical saturation was here applied in a pragmatic way, where the researcher determined when no new issues were identified in three consecutive interviews, but with the awareness that more issues might have been identified had more interviews been carried out.

4.2.4 Time and venue for planned interviews

Two rounds of audio-recorded interviews took place, one shortly (1-2 months) after patients have had their first consultation with a homeopath, and a second interview about 6 months after the first consultation, at which time patients should have had at least 2 follow-up consultations. A maximum of 30 patients were interviewed at each time point. Each interview was planned to last for about 30 to 60 minutes, with flexibility to allow for shorter or longer interviews if needed.

Interviews were carried out in the clinics where patients received treatment by a homeopath or alternatively at the University of Sheffield. The choice of interview venues might affect the outcome of interviews (Elwood & Martin 2000). Interviewees could have felt more or less free to express their opinions depending on where the interview took place, and different interview locations might trigger different memories, thoughts and emotions. Interviews carried out in patients' homes might have provided greater opportunity for them to freely express any negative experiences, as opposed to the clinic where treatment took place. Moreover, interviewees' homes might provide an additional source of information where the researcher could have observed objects in the surroundings or interaction with other people that might add important insight (Elwood & Martin 2000). The reason for carrying out interviews in treatment clinics or in University premises was purely pragmatic, as it was more practical. However, patients were given two different options in order to increase the chance that they could feel free to speak about their experiences with the treatment. They could, if they felt reluctant to talk about negative experiences in the clinic where they had received treatment, chose to be interviewed at the University. On the other hand, carrying out interviews at the University might have increased their feeling of power distance to me as a researcher, although this

might be less problematic in clinics they already were familiar with. Both the University and the clinics are venues where privacy and little distraction could be expected, another characteristic of interview venues that has been stressed as important by other researchers (Gill et al. 2008). This could also have been problematic in patients' homes, if other people had been present in the house. Reflection on the role of the interview venue will be part of the discussion of the results.

I carried out all interviews myself. An interview guide accompanying the ethics application approved by the Regional Ethics Committee was developed for each of the two interviews and can be found in Appendixes 13 (Interview guide I 120620 rev 121017) and 14 (Interview guide II 120620).

4.2.5 The different stages of the qualitative research project

The qualitative study consisted of several stages put into place in order to answer the research question while ensuring patients' rights and integrity and strengthening the trustworthiness of the research. The different analytical stages are in line with suggestions put forward by authors such as Braun & Clarke (2013) and Patton (1990).

Initial patient contact

Patients found to be eligible to participate were to be sent a letter (Appendix 15: Letter to patients – Invitation for qualitative interviews) with information about the study and a consent form (Appendix 16: Consent form). The letter included a brief presentation of the purpose and method of the interview, a consent form and information stating that patients' responses would be treated confidentially, that their participation was voluntary and that they were free to withdraw from the project at any time without giving a reason. They were informed that public transportation expenses would be refunded. Selected participants were contacted by telephone no sooner than two days after having received the offer letter, to hear if they had any questions and if they wanted to participate. A time and place for the interview was agreed for patients who consented to participate.

Audio-recording and interview transcription

Audio-recorded semi-structured interviews were carried out, using as much open-ended questions as possible with an aim to answer the research question. A verbatim transcription of each interview was developed by a professional transcriber. Transcripts were compared with audio-recorded interviews. Any discrepancies changing the meaning of the content were checked by a second researcher. When no consensus was reached, a third researcher was consulted. A majority vote would be used if there was still no consensus in the understanding of interviews.

Revision of the interview guide

After having assessed the first two to three interviews, a decision was made as to whether any of the main questions needed revision, in order to reach any further depth or breadth in participants' responses. This decision was made by two researchers, and in case of disagreement, a third researcher would be consulted to sort out any differences in opinion.

Analytical process with development of codes and themes

Throughout the initial stages I made myself familiar with the data. Each transcript was read repeatedly (at least three times). Throughout this process initial codes and themes were developed. This involved marking interview passages that could be of relevance to answer the research question, with a note containing an initial "code" for each quote. Data not considered relevant were not coded (Braun & Clarke 2013). Codes could be single words or brief sentences that described the essence of what a patient said in a part of the interview. Codes could consist of patients' own words or they could be developed by the researcher, as suggested by Glaser & Strauss (1967). A single statement could be coded by using one or several codes. The relationship between various codes was considered, some could be merged into fewer codes, and others could be expanded to more than a single code. Codes were then sorted so they fitted under overarching themes and where needed sub-themes.

Themes (and sub-themes) were based on codes. Typically, a theme was broader than a code and contained information from several codes. Sub-themes were part of themes, but

to a considerable extent linked to a theme and were therefore not themes in their own right. In some instances a code was changed into a theme. A theme was typically presented by a single word or a short phrase and described using more words and illustrated with quotes from patient interviews.

Codes and themes were re-visited and compared to each other several times throughout the process to determine which ones should be kept, changed, merged, split or excluded. The entire process could be considered to be inclusive (at first with too many rather than too few codes). This could be seen as an organic process which gradually evolved where the researcher went "back and forth" between the interview, the codes and themes, from one interview to another (Braun & Clarke 2013).

A good code should be concise, it should contain what is essential from a particular passage in the interview, and it should be able to stand on its own (separate from the data). Themes should be meaningful, they should be described in such a way that it becomes clear to the reader in what way it answers the research question (Braun & Clarke 2006, 2013), in this case providing a description of patients' experience with treatment provided by homeopaths. Themes could be smaller or larger and did not necessarily have to be of equal size. Each theme should however be able to stand on its own, but also to fit together for an overall understanding of the research question.

The entire analytical process could go on for a considerable length of time, in principle indefinitely. The researcher decided when to stop, partly determined by financial and time constraints. However, it should preferably only take place at saturation, after the themes answering the research question had been developed.

4.2.6 Trustworthiness of the results from the qualitative interview study

In quantitative research "reliability" and "validity" are commonly referred to when assessing the trustworthiness of results. Validity refers to the degree to which for example an outcome measures what it is claimed to measure, and reliability refers to the extent to which the outcome measure performs similarly over time (test-retest reliability) assuming there is no significant change in the tested subject, and the extent to which different

individuals agree on how the outcome should be administered and scored (inter-rater reliability) (Roach 2006). Such an understanding makes less sense in qualitative research where the researcher more actively engages in and influences the research process (Golafshani 2003). Although it might be possible for different researchers to reach similar conclusions when interviewing patients and analysing data in this research project assessing depressed patients' experiences with treatment provided by homeopaths, it might make more sense to determine whether the methods contributed to establish confidence in the results or, in other words, whether the results were trustworthy (Lincoln & Guba 1985, Rodwell & Byers 1997). Trustworthiness could be assessed through the credibility, dependability, confirmability and transferability of the results.

The credibility of the research

Several measures were put into place to strengthen the credibility of the results. The method chosen for this qualitative research was inductive and exploratory (Guest et al. 2012). This means that it was driven by the content, in this case the content of the qualitative interviews with patients who had received treatment by a homeopath. Interviews were carried out until saturation, as described previously.

My own knowledge and experience was likely to influence the results of my research. Wengraf (2001) points out that when we carry out a qualitative interview, we bring our past experiences, our anxieties, our prejudices, our culture, our socioeconomic status, and our hopes for the future to the interview, and so does the person who is interviewed. This also affects us when we analyse the data. There are advantages and disadvantages to this. On one hand, there was a risk that I would draw participants' focus in a particular direction. I needed to do what I could to, as much as possible, ensure that patients' own experiences were presented. On the other hand, my background could contribute positively to the interview process, as I already had knowledge and experience in treating patients suffering from depression with homeopathy, and therefore could address issues and pose follow-up questions I might otherwise not have thought of. The important part here was that I was aware of my own role and kept track of what questions I posed and the reasons for this.

The credibility was also strengthened through the use of interview guides containing the formal procedures and a framework of questions posed at each individual interview. Moreover, patient interviews were to last for up to 60 minutes or longer, depending on patients' needs and the numbers and details of raised topics. Questions posed were as much as possible to be open-ended, as opposed to closed or leading questions. I asked patients, as much as possible, to describe their experience in their own words, avoided the use of "why" questions, and used active listening as described below. Follow-up questions were posed in order to probe for further and deeper understanding of patients' thoughts and experiences. Patients were encouraged to speak openly and honestly about their experiences, by using active listening where the researcher regularly confirms his understanding through verbal (feeding back what the researcher has understood) and non-verbal (e.g. by nodding) communication. Member checking, checking with patients who are interviewed, should be carried out during interviews in order for patients to confirm whether the researcher understood them correctly or to allow patients to correct, adjust or expand on the researcher's understanding. I rephrased questions if I suspected there were any misunderstandings. If, after checking with patients, there were still discrepancies between patients' and my understanding of what they have expressed, then both our understandings were to be included and used as basis for analysis.

It was pointed out, both in the invitation letters sent to patients prior to interviews and at the start of the interviews, that interviews were confidential. Hence, the individual patient could not be identifiable in the published report, so neither the patient's homeopath nor their GP or any other person should be able to identify them, thereby allowing patients to speak more openly and freely.

Furthermore, the credibility of the research was strengthened by the use of verbatim transcriptions by a professional transcriber not otherwise involved in the project, by the researcher comparing transcriptions and audio-recordings, as well as consulting with a second and third researcher in case of identification of any discrepancies.

Analysis of interviews was carried out through several phases and by returning to interviews several times for assessment and re-assessment of the data. This contributed to increasing the likelihood that patients' thoughts, views and experiences were properly reflected in the results, thereby strengthening the credibility of the research.

The codes and themes developed through the research were not predetermined, but developed from the data. The primary purpose of the analysis was, as accurately and comprehensively as possible, to present patients' experiences as reported by patients themselves, in order to answer the research question. Credibility and trustworthiness is linked to meaningfulness of the results, which depends on richness of information gathered through the research (Patton 1990). Themes were presented using as rich descriptions as possible and covered issues that were considered by the researcher to be predominant in the interviews. Descriptions were supported by patients' responses. Opposite or differing views and experiences, whether held by a limited number of patients or even a single patient, were included if considered to be important in answering the research question.

The dependability, confirmability and transferability of the results

Salmon (2013) states that it is not possible to reproduce semi-structured interviews as they are a type of conversation, and collection and analysis of data to a considerable extent depend on the researcher. For these reasons it was particularly important to as clearly as possible describe the qualitative research methods used, to report what was done, and hereunder how interviewees were selected and recruited, and what data that was identified and how it was interpreted. This enables readers to assess the trustworthiness of the results.

It was likely that some changes to interviews would be made throughout the research process. The researcher might for example need to make minor or more considerable alterations to the interview guide depending on experiences gained with previous interviews. The trustworthiness of the results therefore depended on the extent to which these changes were properly documented and understandable.

The confirmability of the results is assessed through the extent to which the results could be traced back to the data. Whether themes are sufficiently supported by the data is illustrated by including patient interview quotes. A report describing the various stages of the research process adds to the trustworthiness.

4.3 Mixed methods to assess patients' experiences

As no previously published qualitative studies reporting on depressed patients' experiences with treatment provided by homeopaths were identified through the systematic review, no studies reporting on any mixed methods were identified either. A mixed methods approach was to be used in order to compare and combine the results of the RCT and the qualitative interview study.

The methods used for the mixed methods approach are described in the following sections, including a brief description of mixed methods and a description of the specific approach (triangulation) chosen to assess the research question.

4.3.1 Why use mixed method to learn from depressed patients' experiences?

This research project includes both quantitative and qualitative methods. Mixed methods combine data collected through quantitative and qualitative research, and can strengthen the power of the findings from the individual parts of the research project (O'Cathain 2009). Greene et al. (1989, p.256) state that mixed method designs "[…] include at least one quantitative method (designed to collect numbers) and one qualitative method (designed to collect words) […]"

The results of a mixed methods approach might contribute to expand our understanding of the research by not simply adding the results of the qualitative and quantitative parts of the project, but also by providing added insight to answer the research questions. The use of mixed methods can be particularly helpful in understanding the results of pragmatic trials (Albright et al. 2013), which was the method used in the quantitative part of this research project.

As pointed out in the introductory chapter of this thesis, the use of mixed methods may be considered appropriate within the framework of pragmatism, as the used qualitative and quantitative methods are not considered to be incompatible, but rather tools used to answer "real world" research questions (Feilzer 2010, Tashakkori & Teddlie 2010). It is hoped that the used mixed methods approach may contribute to enabling translation of the research

results in this project into clinical practice and policy, as suggested by Albright et al. (2013).

4.3.2 The use of triangulation to learn from patients' experiences

There are several ways in which data from qualitative and quantitative research can be integrated, such as following a thread, using a mixed methods matrix and triangulation (O'Cathain 2010). The choice of mixed methods approach depends on several factors, including the research question to be answered, methodological considerations (that contribute to considering which approach is more appropriate or effective in answering the research question) and the resources available (financial, time, manpower, competence).

This research project uses triangulation. The term "triangulation" is here understood as a specific approach to mixed methods research, as suggested by O'Cathain (2010), and is not limited to its interpretation by Greene et al. (1989). In Greene's paper, which has been quoted extensively in the mixed methods literature, the authors understand ***triangulation*** as a purpose of mixed methods research which seeks convergence, corroboration or correspondence of the results using different research methods. Other purposes of mixed methods research include ***complementarity***, which can be understood as elaborating or enhancing the results from one method with the results found using another method; ***development***, which involves the sequential use of different research methods; ***initiation***, where discrepancies or contradictions may offer new perspectives; and ***expansion***, where the aim is to present a wider range of results by the use of different research methods.

In contrast, O'Cathain (2010) presents triangulation not as a purpose of a mixed methods approach, but as a specific approach which can contribute to assessing ***convergence***, i.e. correspondence or agreement in the results found using different research methods; ***complementarity***, where one research method contributes to expanding on the results identified through the other research method; and ***discrepancy*** or ***dissonance***, where findings using one research method contradicts findings of another. Discrepancy or dissonance does not necessarily result in the conclusion that the results of one method are incorrect, but can help by expanding our understanding of each of the two, thereby giving a

more nuanced understanding of the combined results of the qualitative and the quantitative research results.

The results of this research project will be presented sequentially and triangulation applied at the reporting stage. A weakness of this approach was that it was to a smaller extent used to integrate the qualitative and the quantitative parts of the research, as opposed to a more integrated method where the researcher would shift back and forth between the two methods during the analysis stage, as suggested when following a thread (O'Cathain 2009). It was considered to be more feasible than using a mixed methods matrix (O'Cathain 2009) for this research project, as such a method would involve comparison of interviews and questionnaire responses at the individual level. The sequential approach used in triangulation required fewer resources (e.g. financial by using fewer researchers) and it would be less time consuming and feasible within the time constraints of my PhD studies.

In the following chapter the results of the trial, the qualitative study and the mixed methods are presented.

5 Trial results: Depressed patients treated by homeopaths

This chapter presents the results 6 months into the RCT. This will include screening and recruitment of patients, a description of the flow of patients through the study, patients' baseline data, the acceptability, the safety and the effectiveness of the offer of treatment provided by homeopaths for patients with self-reported depression and of the treatment received by these patients.

5.1 Screening and recruitment

Patients included in the trial were recruited through the Yorkshire Health Study (YHS). At the time of recruitment 22,179 patients in the cohort had consented to be contacted again. Out of these 1,917 patients (8.7%) previously reported suffering from long-standing depression (as described in section 4.1.4: Screening and data collection).

The Mood and Health Questionnaire for screening and baseline data collection was sent in September 2013 to the first 200 patients who previously reported long-standing depression. A total of 40 patients (20%) responded. A similar response rate for all 1,917 patients who previously reported long-standing depression would give 383 responses. The estimated attrition rate of 40 % would reduce the number to 230 patients, which would be considerably less than the sample size calculation of 484 patients. Moreover, some of the patients would be likely not to fulfil all inclusion criteria. It was therefore decided that the Mood and Health Questionnaire would be sent to all cohort patients who had previously reported either suffering from long-standing depression (n=104), being moderately or extremely anxious or depressed (on EQ-5D) on the particular day when they completed the previous questionnaire (n=3,823), or both (n=1,813). The baseline Mood and Health Questionnaire was therefore sent to a total of 5,740 patients.

Testing a longer version of the mood and health questionnaire

Half of the 200 patients who were contacted in September 2013 were sent a shorter (6-page) version of the questionnaire and the other half a longer (8-page) version including the Measure Yourself Medical Outcome Profile (MYMOP2) and a life satisfaction score.

Response rates were slightly higher (23% versus 17%) for the 6-page version. Moreover, several responses to the MYMOP2 questionnaire indicated that patients did not understand how the questionnaire was intended to be completed. For these reasons, the 6-page version of the questionnaire was used for all remaining 5,540 patients (sent October 2013). This is also in line with the results of a Cochrane review showing that the odds of response in 56 trials on average increases by more than 60 % when using shorter versions of questionnaires (Edwards et al. 2009).

Data entry checked

Entry of data from questionnaires into an Excel database was carried out by the first researcher (PV). A second researcher (PF) checked the accuracy of all entered data of a random selection of 20 questionnaires (baseline and 6 months). A total of four mistakes were identified for 1,740 items (0.23%). This included two items entered into the neighbour cell in Excel and two incorrect values (2 instead of 3 for one EQ-5D item, and 13 instead of 14 for number of days ill health prevented from carrying out household tasks). No mistakes were found for entry of PHQ-9 or GAD-7 data. Assuming 0.23 % is a representative rate for the overall data set (baseline n=566, 6 months n=458), this would give a total of 206 mistakes for 89,844 items.

The final response rate to the Mood and Health Questionnaire

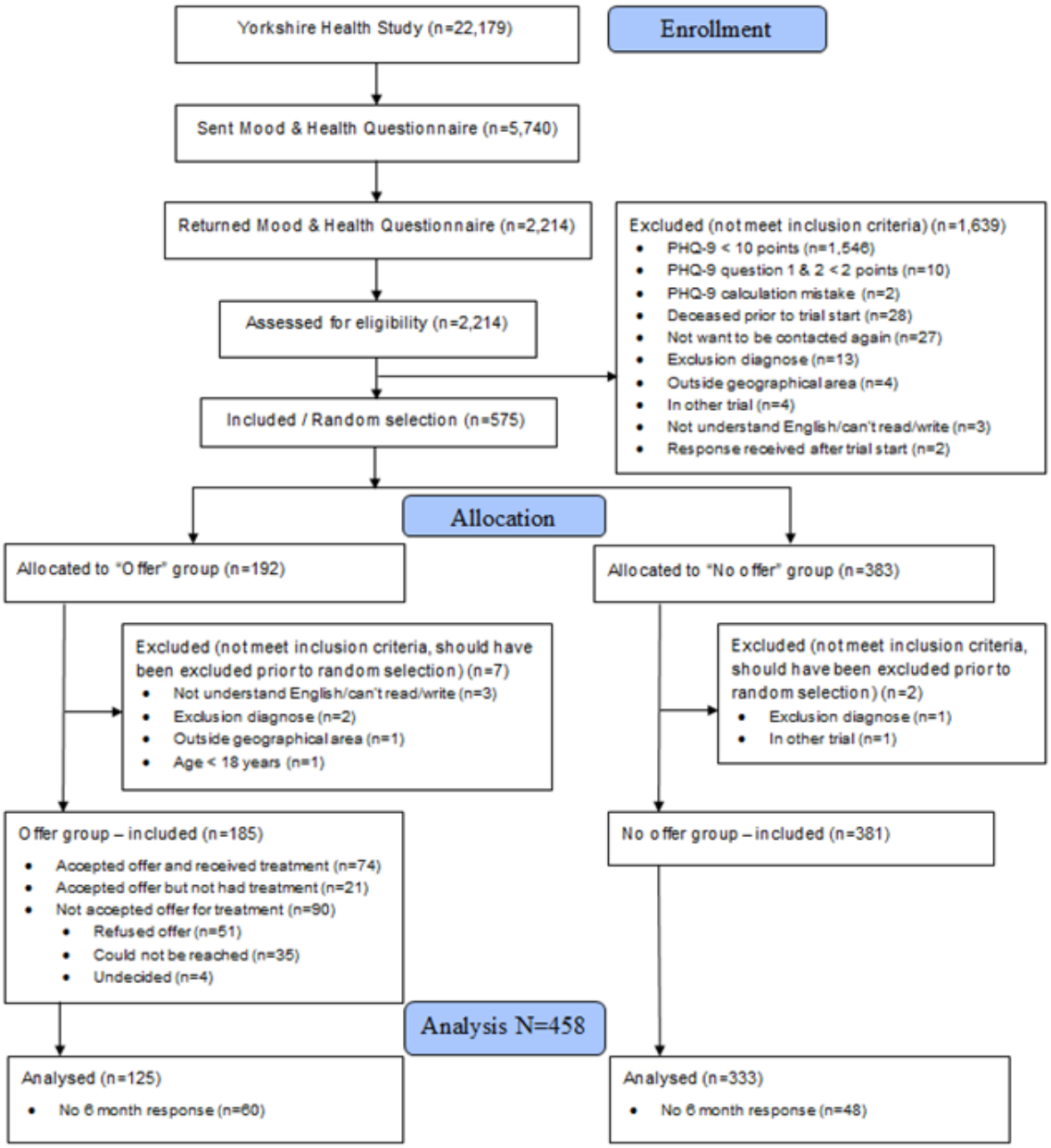
Out of 5,740 letters sent to patients, 2,214 Mood and Health Questionnaires were completed and returned, giving a 38.6 % response rate.

5.2 Inclusion and exclusion criteria

Out of 2,214 responses, 1,639 were excluded as they did not meet the inclusion criteria. The main reason for non-inclusion (94.3%) was a total PHQ-9 score below 10 points, the threshold set for moderate depression. The remaining 575 patients were included for random selection. It was later found that nine patients should not have been included for random selection as they did not fulfil the inclusion/exclusion criteria for the following reasons: exclusion diagnoses (n=3) (Alzheimer's disease, bipolar disorder, psychotic),

unable to understand English or unable to read or write (n=3), included in another trial (n=1), lived outside the geographical area (n=1), or were under 18 years of age (n=1). This left 566 patients in the trial. The flow of patients together with a complete list of reasons for exclusion may be found in figure 2 (Flow of patients in the randomised controlled trial).

Figure 2. Flow of patients in the randomised controlled trial



5.3 Random selection

A rolling recruitment procedure was used. Random selection therefore took place three times, on 9 December 2013 (n=514), on 14 January 2014 (n=58) and on 7 February 2014 (n=3). Two patients who responded later were not included, as 7 February was chosen as an inclusion cut-off date. Random selection was carried out by another researcher (Dr Mark Strong) who was not otherwise involved in the trial. Only patients' ID numbers (and no other patient information) were sent to this researcher. Random selection was carried out using an unequal randomisation ratio (1:2 for the Offer group:No offer group) with a random number generator. Results of the random selection process were returned to the Chief Investigator (PV) who arranged for the letters with the offer of treatment and consent forms to be sent to all "Offer" group patients.

5.4 Baseline characteristics of cohort participants included in the trial

Baseline data for patients overall and for the "Offer" group and "No offer" group may be found in tables 10 (Randomised controlled trial: Baseline demographics), 11 (Randomised controlled trial: Baseline health measures) and 12 (Randomised controlled trial: Baseline medication and treatment). Baseline data show that "Offer" group and "No offer" group patients were comparable for all demographic characteristics, health measures and baseline medication and treatment.

5.4.1 Demographics of patients

The mean age of the 566 patients included in the trial was 54.5 years (SD 14.6), similar to cohort patients overall (54.4 years) (data not shown). More than two thirds were in their 40s, 50s or 60s. Six out of ten were female (details in table 10), which was slightly more than cohort patients overall (56.2%) (Green et al. 2014).

Table 10. Randomised controlled trial: Baseline demographics

					Treatment arm					
		Total			No offer group (usual care group)			Offer group (usual care + treatment by a homeopath)		
Variable		**n**	**Mean / %**	**SD / % of responders**	**n**	**Mean / %**	**SD**	**n**	**Mean / %**	**SD**
Gender	Female	343	60.6 %	60.6 %	229	60.1 %		**114**	**61.6 %**	
	Male	223	39.4%	39.4%	152	39.9%		**71**	**38.4%**	
Age		566	54.5	(14.6)	381	53.9	(14.4)	**185**	**55.8**	**(15.0)**
Age category	18 – 19	4	0.7 %	0.7 %	2	0.5 %		**2**	**1.1 %**	
	20 – 29	35	6.2 %	6.2 %	25	6.6 %		**10**	**5.4 %**	
	30 – 39	59	10.4 %	10.5 %	44	11.5 %		**15**	**8.1 %**	
	40 – 49	98	17.3 %	17.4 %	68	17.8 %		**30**	**16.2 %**	
	50 – 59	159	28.1 %	28.2 %	103	27.0 %		**56**	**30.3 %**	
	60 – 69	126	22.3 %	22.3 %	87	22.8 %		**39**	**21.1 %**	
	70 – 79	73	12.9 %	12.9 %	46	12.1 %		**27**	**14.6 %**	
	80 – 85	10	1.8%	1.8%	4	1.0 %		**6**	**3.2 %**	
		564	99.5 %	100.0 %	379	99.5 %		**185**	**100.0 %**	
Children ≤ 2 years	Yes	24	4.2 %		15	3.9 %		**9**	**4.9 %**	
Pregnant	Yes	4	0.7 %		4	1.0 %		**0**	**0.0 %**	
Ethnic group	British	543	95.9 %	96.3 %	364	95.5 %		**179**	**96.8 %**	
	Non-British	21	3.7 %	3.7 %	15	3.9 %		**6**	**3.2 %**	
		564	99.6 %	100.0 %	379	99.5 %		**185**	**100.0 %**	
City/Borough	Barnsley	56	9.9 %	9.9 %	38	10.0 %		**18**	**9.7 %**	
	Doncaster	139	24.6 %	24.6 %	92	24.1 %		**47**	**25.4 %**	
	Rotherham	115	20.3 %	20.4 %	82	21.5 %		**33**	**17.8 %**	
	Sheffield	254	44.9 %	45.0 %	168	44.1 %		**86**	**46.5 %**	
		564	99.6 %	100.0 %	380	99.7 %		**184**	**99.5 %**	
Employed	Yes	216	38.2 %	40.3 %	152	39.9 %		**64**	**34.6 %**	
	No	320	56.5 %	59.7 %	209	54.9 %		**111**	**60.0 %**	
		536	94.7 %	100.0 %	361	94.8 %		**175**	**94.6 %**	
IMD quintile	1 (least deprived)	32	5.7 %	5.7 %	21	5.5 %		**11**	**5.9 %**	
	2	110	19.4 %	19.4 %	76	19.9 %		**34**	**18.4 %**	
	3	81	14.3 %	14.3 %	55	14.4 %		**26**	**14.1 %**	
	4	107	18.9 %	18.9 %	73	19.2 %		**34**	**18.4 %**	
	5 (most deprived)	236	41.7 %	41.7 %	156	40.9 %		**80**	**43.2 %**	
		566	100.0 %	100.0 %	381	100.0 %		**185**	**100.0 %**	

Table 11. Randomised controlled trial: Baseline health measures

					Treatment arm					
		Total			No offer group (usual care group)			Offer group (usual care + treatment by a		
Variable		**n**	**Mean / %**	**SD / % of responders**	**n**	**Mean / %**	**SD**	**n**	**Mean / %**	**SD**
PHQ-9 score		566	17.0	(4.6)	381	17.0	(4.6)	185	**16.9**	**(4.5)**
PHQ-9 category	Moderate (10 – 14)	197	34.8 %	34.8 %	133	34.9 %		**64**	**34.6 %**	
	Moderately severe (15 – 19)	202	35.7 %	35.7 %	133	34.9 %		**69**	**37.3 %**	
	Severe (20 – 27)	167	29.5 %	29.5 %	115	30.2 %		**52**	**28.1 %**	
		566	100.0	100.0%	381	100.0		**185**	**100.0**	
Depression onset	Acute (< 3 months)	6	1.1 %	1.5 %	4	1.0 %		**2**	**1.1 %**	
	Subacute (3 months - < 1 year)	19	3.4 %	4.9 %	14	3.7 %		**5**	**2.7 %**	
	Chronic (short) (1 - < 2 years)	51	9.0 %	13.0 %	39	10.2 %		**12**	**6.5 %**	
	Chronic (long) (2 - < 5 years)	41	7.2 %	10.5 %	31	8.1 %		**10**	**5.4 %**	
	Chronic (very long) (5 years +)	274	48.4 %	70.1 %	185	48.6 %		**89**	**48.1 %**	
		391	69.1 %	100.0 %	273	71.7 %		**118**	**63.8 %**	
Depression episode onset	Acute (< 3 months)	34	6.0 %	15.0 %	24	6.3 %		**10**	**5.4 %**	
	Subacute (3 months - < 1 year)	33	5.8 %	14.5 %	25	6.6 %		**8**	**4.3 %**	
	Chronic (short) (1 - < 2 years)	22	3.9 %	9.7 %	13	3.4 %		**9**	**4.9 %**	
	Chronic (long) (2 - < 5 years)	19	3.4 %	8.4 %	11	2.9 %		**8**	**4.3 %**	
	Chronic (very long) (5 years +)	22	3.9 %	9.7 %	13	3.4 %		**9**	**4.9 %**	
	Chronic (length unspecified)	76	13.4 %	33.5 %	46	12.1 %		**30**	**16.2 %**	
	Periodic	17	3.0 %	7.5 %	14	3.7 %		**3**	**1.6 %**	
	None	4	0.7 %	1.8 %	3	0.8 %		**1**	**0.5 %**	
		227	40.1 %	100 %	149	39.1 %		**78**	**42.2 %**	
GAD-7 score		564	13.7	(4.8)	380	13.8	(4.8)	**184**	**13.4**	**(4.8)**
GAD-7 category	Normal (0 – 4)	20	3.5 %	3.5 %	14	3.7 %		**6**	**3.2 %**	
	Mild (5 – 9)	91	16.1 %	16.1 %	59	15.5 %		**32**	**17.3 %**	
	Moderate (10 – 14)	194	34.3 %	34.4 %	126	33.1 %		**68**	**36.8 %**	
	Severe (15 – 21)	259	45.8 %	45.9 %	181	47.5 %		**78**	**42.2 %**	
		564	99.6 %	100.0 %	380	99.7 %		**184**	**99.5 %**	
BMI score		513	28.18	(6.63)	353	28.13	(6.66)	**160**	**28.31**	**(6.56)**
BMI category	Underweight (< 18.5)	11	1.9 %	2.1 %	8	2.1 %		**3**	**1.6 %**	
	Healthy weight (18.5 – 24.9)	187	33.0 %	36.5 %	129	33.9 %		**58**	**31.4 %**	
	Overweight (25.0 – 29.9)	135	23.9 %	26.3 %	98	25.7 %		**37**	**20.0 %**	
	Obese (30.0 – 39.9)	149	26.3 %	29.0 %	98	25.7 %		**51**	**27.6 %**	
	Morbidly obese (40.0 +)	31	5.5 %	5.5 %	20	5.2 %		**11**	**5.9 %**	
		513	90.6 %	100.0 %	353	92.7 %		**160**	**86.5 %**	
Long-standing conditions	Yes	515	91.0 %	92.5 %	350	91.9 %		**165**	**89.2 %**	
	No	42	7.4 %	7.5 %	25	6.6 %		**17**	**9.2 %**	
		557	98.4 %	100.0 %	375	98.4 %		**182**	**98.4 %**	
Long-standing conditions	Score	557	3.02	(1.79)	375	3.03	(1.80)	**182**	**3.01**	**(1.77)**
Long-standing conditions	0-3 conditions	352	62.2 %	63.2 %	235	61.7 %		**117**	**63.2 %**	
	> 3 conditions	205	36.2 %	36.8 %	140	36.7 %		**65**	**35.1 %**	
		557	98.4 %	100.0 %	375	98.4 %		**182**	**98.4 %**	
Alcohol consumption	Days last week	541	1.73 /	(2.76)	365	1.76	(2.64)	**176**	**1.65**	**(2.99)**
	Units last week	537	7.43 /	(15.47)	363	7.65	(15.02)	**174**	**6.98**	**(16.41)**

Table 12. Randomised controlled trial: Baseline medication and treatment

					Treatment arm					
		Total			No offer group (usual care group)			Offer group (usual care + treatment by a homeopath)		
Variable		**n**	**%**	**% of responders**	**n**	**Mean / %**	**SD**	**n**	**Mean / %**	**SD**
Antidepressant use (current)	Yes	236	41.7 %	99.6 %	155	40.7 %		**81**	**43.8 %**	
	No	1	0.2 %	0.4 %	1	0.3 %		**0**	**0.0 %**	
	Unknown	329	58.1 %		225	59.1 %		**104**	**56.2 %**	
		566	100.0 %	100.0 %	381	100.0 %		**185**	**100.0 %**	
Antidepressant use (past)	Yes	337	59.5 %	65.6 %	234	61.4 %		**103**	**55.7 %**	
	No	177	31.3 %	34.4 %	124	32.5 %		**53**	**28.6 %**	
	Unknown	52	9.2 %		23	6.0 %		**29**	**15.7 %**	
		566	100.0 %	100.0 %	381	100.0 %		**185**	**100.0 %**	
Medication (all types)		559	98.8 %			4.65	(3.86)		**4.66**	**(3.95)**
Hospital A&E		261	46.1 %			0.36	(0.62)		**0.47**	**(1.60)**
Hospital day case		242	42.8 %			0.36	(0.85)		**0.48**	**(1.60)**
Hospital outpatients		338	59.7 %			1.22	(2.03)		**1.43**	**(2.45)**
Hospital in-patients (nights)		234	41.3 %			0.83	(2.92)		**0.62**	**(2.24)**
GP		474	83.7 %			2.48	(2.39)		**2.95**	**(5.61)**
Nurse		355	62.7 %			1.44	(2.38)		**1.92**	**(6.21)**
Physiotherapist		236	41.7 %			0.64	(1.84)		**0.96**	**(2.57)**
Dietitian		217	38.3 %			0.14	(0.63)		**0.33**	**(1.64)**
Midwife		209	36.9 %			0.03	(0.27)		**0.11**	**(0.95)**
Mental health worker		233	41.2 %			0.76	(2.42)		**0.43**	**(1.48)**
Psychotherapist		220	38.9 %			0.39	(1.49)		**0.28**	**(1.60)**
Counsellor		237	41.9 %			0.77	(2.94)		**0.55**	**(1.64)**
Care worker		214	37.8 %			0.31	(1.83)		**0.03**	**(0.24)**
Social worker		215	38.0 %			0.08	(0.44)		**0.07**	**(0.42)**
Health visitor		214	37.8 %			0.57	(5.12)		**0.11**	**(0.59)**
Community health champion		210	37.1 %			0.04	(0.30)		**0.00**	**(0.00)**
Health trainer		213	37.6 %			0.55	(5.13)		**0.19**	**(1.19)**
Acupuncturist		217	38.3 %			0.19	(0.78)		**0.13**	**(0.67)**
Chiropractor		214	37.8 %			0.22	(0.97)		**0.22**	**(1.24)**
Herbalist		210	37.1 %			0.04	(0.22)		**0.01**	**(0.12)**
Homeopath		206	36.4 %			0.00	(0.00)		**0.00**	**(0.00)**
Osteopath		210	37.1 %			0.16	(1.16)		**0.04**	**(0.26)**

Patients included in the trial were much more likely to live in the most deprived areas of South Yorkshire (IMD quintile 5: 41.7%) compared to those contacted for screening for the trial (30.8%), compared to responders who did not fulfil the inclusion criteria (21.7%) (data not shown), compared to cohort participants overall (25.1%) and the general population (34.8%) (Green et al. 2014). Over 60 % belonged to the two highest (out of 5) deprivation groups. More than half (56.5%) were unemployed whereas 38.2 % reported being employed.

As for the cohort overall, the vast majority of trial patients were of White ethnicity, with less than five percent of non-British ethnic origin. Most patients included in the trial were

from Sheffield and the surrounding areas (44.9%), whereas 24.6 % were from Doncaster, 20.3 % from Rotherham and 9.9 % from Barnsley. Only four out of 566 patients were pregnant and 24 patients had children aged 2 years or less. We may therefore assume that most depressed patients did not suffer from post-partum depression.

In summary, the average age of trial patients was about 55 years and they were more likely to be female than male, and mostly of British origin. Their age was comparable to cohort patients overall, but they were slightly more likely to be female and to live in more deprived areas than other patients in the cohort and in the general population.

5.4.2 Patients' health measures at baseline

Patients' depression scores (PHQ-9)

Patients' PHQ-9 depression scores at baseline were fairly equally distributed between the three severity groups, with somewhat fewer in the "severe" category (29.5%) compared to "moderate" (34.8%) and "moderately severe" (35.7%). The "Offer" and "No offer" groups were similarly distributed between the three categories. The mean baseline PHQ-9 score was 17.0 (SD 4.6) (with no imputation for missing data and calculation of PHQ-9 sum scores for all patients, also those who did not respond to all PHQ-9 questions), with 17.0 (SD 4.6) for the "No offer" and 16.9 (SD 4.5) for the "Offer" group (on a 0–27 point scale where moderate depression is in the range from 10-14 points, moderately severe from 15-19 points, and severe depression from 20-27).

Seventy percent of patients responded to the question about the onset of depression and 40 % responded to the question about the onset of the current episode of depression. The majority of patients (93.6%) responding to the question about the onset of their depression suffered from what could be considered to be chronic, long-standing depression (lasting at least one year) (64.6% of all patients when including non-responders to this question). For 70.1 % of patients depression started at least five years earlier (48.4% when including non-responders). Only 1.5 % could be categorised as acute (< 3 months' duration) and 4.9 % as sub-acute depression (3 months – < 1 year). Almost one third of patients did not report

when depression first started. Forty percent of patients reported the onset of the current depression episode, with 61 % of patients stating that depression had lasted for at least one year (chronic depression) (24.6% of all patients). In 15.0 %, the current episode could be categorised as acute (< 3 months), in 14.5 % sub-acute (3 months – < 1 year), in 7.5 % periodic and 1.8 % stated they were not currently depressed, although their PHQ-9 scores suggested at least moderate depression. "Offer" and "No offer" group patients were comparable with regards to the onset of depression and the onset of the current episode.

In summary, patients suffered from long-standing moderate, moderately severe or severe depression. "Offer" and "No offer" group patients were comparable with regards to depression scores and categories, onset of depression and onset of the current episode of depression.

Patients' anxiety scores (GAD-7)

Patients' baseline mean anxiety score (GAD-7) was 13.7 points (SD 4.8), with 13.8 points (SD 4.8) for the "No offer" group and 13.4 (SD 4.8) for the "Offer" group (0–21 point scale). Almost half (47.1%) reported severe anxiety on the Generalized Anxiety Disorder (GAD-7) scale, whereas 34.3 % were moderately anxious. Only 16.1 % were mildly anxious and 3.5 % were not anxious at all. Higher anxiety scores were significantly correlated to higher depression scores (Pearson's $r=0.581$, $p<0.01$).

In summary, over 80 % of patients suffered from moderate or severe anxiety, and anxiety was correlated to depression scores. "Offer" and "No offer" group patients were comparable with regards to anxiety score and categories.

Other health measures

On the screening and baseline data questionnaire patients were asked if they suffered from any long-standing conditions. Four conditions were specified in the questionnaire (tiredness/fatigue, insomnia, anxiety/nerves, depression), in addition to the category "Other" where patients were asked to give further description. Most patients (91.0%) reported some long-standing condition with more than one third reporting more than three long-standing conditions. The mean number of long-standing conditions was 3.03 (SD

1.80) in the "No offer" group compared to 3.01 (SD 1.77) in the "Offer" group. Higher depression scores were significantly correlated to a higher number of long-standing conditions (Pearson's r=0.245, p<0.001).

The mean body mass index (BMI) score was 28.18 (SD 6.63), with 28.13 (SD 6.66) for the "No offer" group, compared to 28.31 (SD 6.56) for the "Offer" group. More than half of all patients were overweight, obese or morbidly obese, with 31.8 % who were obese or morbidly obese. Higher BMI scores were significantly correlated to higher depression scores (Pearson's r=0.113, p=0.010).

Patients in the "No offer" group had consumed 7.65 units of alcohol (SD 15.02) on average over the last week at the time of completing the questionnaire, compared to 6.98 (SD 16.41) in the "Offer" group. Reported alcohol consumption was not significantly correlated to depression scores (Pearson's r=-0.002, p=0.967).

In summary, nine out of ten patients suffered from long-standing conditions and over half of the patients were overweight or obese. A higher number of comorbidities and obesity was correlated to depression scores, whereas patients' alcohol consumption was not. "Offer" and "No offer" group patients were comparable with regards to the number of long-standing conditions, BMI, alcohol consumption.

5.4.3 Patients' use of medication and other treatment at baseline

Patients were taking an average of 4.65 (SD 3.89) different types of medicines, with 4.65 (SD 3.86) in the "No offer" group and 4.66 (SD 3.95) in the "Offer" group. Use of a higher number of medicines was correlated to higher depression scores (Pearson's r=0.142, p=0.001). The use of antidepressants was however not correlated to depression scores (Pearson's r=-0.043, p=0.511). Antidepressants were used by 41.7 % at the time of completing the questionnaire (unknown for 58.1%) and 59.5 % had used antidepressants in the past (unknown for 9.2%).

The healthcare practitioners most commonly used over the past 3 months were general practitioners (GPs) with an average of 2.48 consultations (SD 2.39), followed by 1.44

consultations (SD 2.38) with a nurse for the "No offer" group, compared to 2.95 (SD 5.61) and 1.92 (SD 6.21) for the "Offer" group. Higher GP use (Pearson's r=0.135, p=0.003) was correlated to higher depression scores, whereas the use of a nurse was not. The "Offer" and "No offer" group were comparable with regards to the frequency of use of healthcare services.

The most common mental health services used over the past 3 months were mental health workers and counsellors, with 0.76 (SD 2.42) and 0.77 (SD 2.94) consultations for the "No offer" group and 0.43 (SD 1.48) and 0.55 (SD 1.64) for the "Offer" group. Psychotherapists were less commonly used, with 0.39 (SD 1.49) and 0.28 (SD 1.60) consultations for the "No offer" and "Offer" group respectively. A higher use of mental health workers and counsellors was significantly correlated to higher depression scores (Pearson's r=0.222, p=0.001; Pearson's r=0.168, p=0.009), whereas the use of a psychotherapist was not.

Hospital services were most commonly outpatient clinics with 1.22 consultations (SD 2.04) in the "No offer" group, compared to 1.43 (SD 2.45) in the "Offer" group over a 3 month period. Outpatient clinics were not significantly correlated to patients' depression scores, whereas hospital in-patient nights and A&E services were (Pearson's r=0.135/0.153, p=0.039/0.013). There were however fewer in-patient nights (0.83/0.62 in the "No offer" and "Offer" group respectively) compared to outpatient consultations, and even fewer hospital A&E and day case consultations.

Alternative practitioners had been used to a limited extent over the past 3 months, with chiropractors (mean 0.22 for both groups) and acupuncturists (mean 0.19 and 0.13 for the "No offer" and "Offer" group) being the most common. Other CAM practitioners were rarely used and homeopaths had not been used at all, as consultations with a homeopath over the past 3 months was an exclusion criterion.

In summary, patients reported using an average of 4 to 5 different types of medications and more than 40 % were taking antidepressants. Use of medication was correlated to higher depression scores, although this was not found for antidepressants. The most commonly used health service was general practitioners (GPs), with almost one consultation every month on average, followed by nurses who were seen approximately once every six weeks.

Visits to outpatient hospital clinics were almost as common as visits by nurses. The use of other healthcare services and alternative practitioners was less common. Higher use of GPs, mental health workers and counsellors was correlated to higher depression scores, whereas the use of nurses and psychotherapists was not. "Offer" and "No offer" group patients were comparable with regards to use of medications and healthcare services.

5.5 Acceptability of treatment by homeopaths for depressed patients

Out of the 185 patients in the "Offer" group, 74 (40%) accepted the offer and had at least one consultation with a homeopath, which was the definition for having received treatment by a homeopath. An additional 21 accepted the offer of treatment, but did not agree a time for a consultation (n=17) or did not appear for their first consultation (n=4).

Patients who did not accept the offer of treatment

A total of 90 patients either refused the offer (n=51), were undecided (n=4) or could not be reached (n=35). Out of the 35 patients who could not be reached, 23 did not respond to telephone, email or reminder letters; no telephone number or email address was known for 10 patients and they did not respond to reminder letters; and two patients died prior to being contacted.

Most of the 51 patients who declined the offer of treatment by a homeopath did not give a reason (n=31). Half of the remaining 20 patients had some health-related reason why they declined the offer, including too poor state of health (n=7), recent bereavement (n=1), not wanting to interfere with ongoing medical treatment (n=1) and waiting for upcoming surgery (n=1). For the remaining 10 patients reasons included logistics (mostly insufficient time) (n=4), "not interested" (n=2), "don't feel I need it" (n=1), "don't believe in homeopathy" (n=1), previous unsuccessful homeopathic treatment (n=1) and "no treatment can help" due to external (financial) circumstances (n=1).

In summary, four out of ten patients accepted the offer and had at least one consultation. Non-accepters either refused the offer, several for health-related reasons, or they could not be reached.

5.6 Patients' responses to the 6 month Mood and Health Questionnaire

All 566 patients included in the trial were sent letters with the follow-up Mood and Health Questionnaire in the first half of May 2014, about 6 months after having received the baseline questionnaire, with reminders for non-responders in June and July. A total of 458 (81%) responded to postal questionnaires (n=455) or telephone contact (n=3). Out of these, 345 postal questionnaire responses (75%) were received within one month, about 6 months post-randomisation. An additional 101 patients (22%) responded to reminders sent in June and nine (2%) in July. Out of the 111 patients who did not respond to postal questionnaires, phone numbers were known for 77 patients, of whom 37 were reached and three completed questionnaires over the telephone with another researcher (PF). Telephone calls were made according to the protocol, shortly after sending the last reminders.

Responses to 6 month follow-up questionnaires were unequally divided between the trial groups. The "No offer" group included 333 of 381 (87%) responses, compared to 125 of 185 patients (68%) in the "Offer" group. The lower proportion of non-responders in the "Offer" group was accounted for by patients who had not received treatment (non-accepters). In the "Offer" group, 65 out of 74 patients (88%) who had received treatment by a homeopath responded to the 6 month questionnaires, compared to only 60 out of 111 patients (54%) who were not treated by homeopaths.

For statistical analyses to be carried out, in particular for assessing the complier average causal effect (CACE), comparability of questionnaire responders and non-responders in the "Offer" group was assessed, as described in section 4.1.14 (The effectiveness of treatment provided by homeopaths for depressed patients).

In summary, more than 80 % of the patients included in the trial responded to the 6 month follow-up questionnaire. The proportion of non-responders was significantly higher for those patients in the "Offer" group who had not taken up the offer. It was therefore necessary to compare baseline differences for "Offer" and "No offer" group responders and non-responders at 6 months.

5.7 Comparability of responders and non-responders in the "Offer" and "No offer" groups at 6 months

Due to differences in questionnaire response rates, baseline data for 6 month responders and non-responders in the "Offer" and "No offer" groups were compared. The comparability of the four groups ("Offer" and "No offer" group responders and non-responders at 6 months) was assessed by using a multiple linear regression model. It included, for each baseline covariate, the constant, the treatment group ("Offer" group and "No offer" group), response status (patients with and without PHQ-9 scores for 6 month assessment) and a ***treatment group x response status interaction term*** as explanatory variables (Walters 2009). For example, this was for the PHQ-9 score at baseline:

$$PHQ\text{-}9_{Baseline} = b_0 + b_{1(Group)} + b_{2(Responder)} + b_{3(Interaction)}$$

b_0 = constant

b_1Group = "Offer" group and "No offer" group

b_2Responder = Patients with and patients without PHQ-9 scores for 6 month assessment

b_3Interaction = Treatment group ("Offer" group=1, "No offer" group=0) x response status interaction (Patients with 6 month PHQ-9 scores=1, Patients without 6 month PHQ-9 scores=0)

Results of these comparisons are presented in tables 13 (Randomised controlled trial: Baseline demographics for offer & no offer group, responders & non-responders at 6 months), 14 (Randomised controlled trial: Baseline health measures for offer & no offer group, responders & non-responders at 6 months) and 15 (Randomised controlled trial: Baseline medication/treatment offer/no offer group, responders/non-resp. at 6 months).

There was little evidence to suggest that there were significant between-group baseline differences in depression and anxiety outcome measures, when comparing baseline data for "Offer" and "No offer" group responders and non-responders at 6 months (p-values for the interaction term ranged from 0.248 to 0.693). This included patients' baseline depression (PHQ-9) and anxiety (GAD-7) scores and categories, and the onset of depression (both first time and current episode). The same was found for patients' BMI scores, alcohol consumption (days and units of alcohol), number of medications used, the existence of long-standing conditions (yes/no), ethnic group, and city/borough (p-values ranging from 0.094 to 0.843) (details tables 13, 14 and 15). There was also limited evidence to suggest

that "No offer" group non-responders at 6 months were more likely to be women compared to the other three groups ($p>0.05$).

Table 13. Randomised controlled trial: Baseline demographics for offer & no offer group, responders & non-responders at 6 months

		Treatment arm								
		No offer group				**Offer group**				
		Response at 6 months		**No response at 6 months**		**Response at 6 months**		**No response at 6 months**		
Variable		**n**	**Mean (SD) %**	**n**	**Mean (SD) %**	**n**	**Mean (SD) %**	**n**	**Mean (SD) %**	**p-value***
Gender	Female	195	58.6 %	34	70.8 %	**80**	**64.0 %**	**34**	**56.7 %**	**0.069**
	Male	138	41.4 %	14	29.2 %	**45**	**36.0 %**	**26**	**43.3 %**	
Age		331	55.1 (13.9)	48	45.4 (15.1)	**125**	**56.2 (13.4)**	**60**	**54.9 (18.0)**	**0.008**
Ethnic group	British	317	95.2 %	47	97.9 %	**119**	**95.2 %**	**60**	**100.0 %**	**0.525**
	Non-	14	4.2 %	1	2.1 %	**6**	**4.8 %**	**0**	**0.0 %**	
	Unknown	2	0.6 %	0	0.0 %	**0**	**0.0 %**	**0**	**0.0 %**	
City / Borough	Barnsley	31	9.3 %	7	14.6 %	**14**	**11.2 %**	**4**	**6.7 %**	**0.409**
	Doncaster	76	22.8 %	16	33.3 %	**24**	**19.2 %**	**23**	**38.3 %**	
	Rotherha	75	22.5 %	7	14.6 %	**28**	**22.4 %**	**5**	**8.3 %**	
	Sheffield	151	45.3 %	17	35.4 %	**59**	**47.2 %**	**27**	**45.0 %**	
	Unknown	0	0.0 %	1	2.1 %	**0**	**0.0 %**	**1**	**1.7 %**	
Employed	Yes	127	38.1 %	25	52.1 %	**48**	**38.4 %**	**16**	**26.7 %**	**0.015**
	No	189	56.8 %	20	41.7 %	**71**	**56.8 %**	**40**	**66.7 %**	
	Unknown	17	5.1 %	3	6.3 %	**6**	**4.8 %**	**4**	**6.7 %**	
IMD quintile	1 (least deprived)	21	6.3 %	0	0.0 %	**6**	**4.8 %**	**5**	**8.3 %**	**0.007**
	2	74	22.2 %	2	4.2 %	**26**	**20.8 %**	**8**	**13.3 %**	
	3	49	14.7 %	6	12.5 %	**14**	**11.2 %**	**12**	**20.0 %**	
	4	58	17.4 %	15	31.3 %	**23**	**18.4 %**	**11**	**18.3 %**	
	5 (most deprived)	131	39.3 %	25	52.1 %	**56**	**44.8 %**	**24**	**40.0 %**	
	Unknown	0	0.0 %	0	0.0 %	**0**	**0.0 %**	**0**	**0.0 %**	

* Significance test for the Treatment group x Responder interaction. Group: "Offer" and "No offer" group. Responder: Patients with and without response to 6 month questionnaire. Interaction: Treatment group ("Offer" group = 1, "No offer" group = 0) x Responder (patients with 6 month response = 1, patients without 6 month response = 0)

Table 14. Randomised controlled trial: Baseline health measures for offer & no offer group, responders & non-responders at 6 months

		Treatment arm								
		No offer group				Offer group				
		Response at 6 months		Response at 6 months		Response at 6 months		Response at 6 months		
Variable		**n**	**Mean (SD) %**	**n**	**Mean (SD) %**	**n**	**Mean (SD) %**	**n**	**Mean (SD) %**	**p-value***
PHQ-9 score			17.0 (4.7)		17.0 (4.2)		**16.6 (4.6)**		**17.6 (4.2)**	**0.270**
PHQ-9 category	Moderate	116	34.8 %	17	35.4 %	**48**	**38.4 %**	**16**	**26.7 %**	**0.289**
	Moderately severe	116	34.8 %	17	35.4 %	**44**	**35.2 %**	**25**	**41.7 %**	
	Severe	101	30.3 %	14	29.2 %	**33**	**26.4 %**	**19**	**31.7 %**	
Depression onset	Acute (<3 months)	4	1.2 %	0	0.0 %	**2**	**1.6 %**	**0**	**0.0 %**	**0.416**
	Subacute (3 mo.- <1 yr)	12	3.6 %	2	4.2 %	**5**	**4.0 %**	**0**	**0.0 %**	
	Chronic (short) (1 - < 2 years)	34	10.2 %	5	10.4 %	**11**	**8.8 %**	**1**	**1.7 %**	
	Chronic (long) (2 - < 5 years)	28	8.4 %	3	6.3 %	**5**	**4.0 %**	**5**	**8.3 %**	
	Chronic (very long)	163	48.9 %	22	45.8 %	**70**	**56.0 %**	**19**	**31.7 %**	
	Unknown	92	27.6 %	16	33.3 %	**32**	**25.6 %**	**35**	**58.3 %**	
Depression episode onset	Acute (<3 months)	24	7.2 %	0	0.0 %	**9**	**7.2 %**	**1**	**1.7 %**	**0.248**
	Subacute (3 mo.- <1 yr)	23	6.9 %	2	4.2 %	**7**	**5.6 %**	**1**	**1.7 %**	
	Chronic (short) (1 - < 2 years)	13	3.9 %	0	0.0 %	**5**	**4.0 %**	**4**	**6.7 %**	
	Chronic (long) (2 - < 5 years)	10	3.0 %	1	2.1 %	**6**	**4.8 %**	**2**	**3.3 %**	
	Chronic (very long)	10	3.0 %	3	6.3 %	**6**	**4.8 %**	**3**	**5.0 %**	
	Chronic (unspecified)	45	13.5 %	1	2.1 %	**23**	**18.4 %**	**7**	**11.7 %**	
	Periodic	10	3.0 %	4	8.3 %	**3**	**2.4 %**	**0**	**0.0 %**	
	None	3	0.9 %	0	0.0 %	**1**	**0.8 %**	**0**	**0.0 %**	
	Unknown	195	58.6 %	37	77.1 %	**65**	**52.0 %**	**42**	**70.0 %**	
GAD-7 score			13.7 (4.8)		14.3 (4.4)		**13.1 (5.0)**		**14.2 (4.2)**	**0.553**
GAD-7 category	Normal	14	4.2 %	0	0.0 %	**5**	**4.0 %**	**1**	**1.7 %**	**0.693**
	Mild	52	15.6 %	7	14.6 %	**24**	**19.2 %**	**8**	**13.3 %**	
	Moderate	109	32.7 %	17	35.4 %	**46**	**36.8 %**	**22**	**36.7 %**	
	Severe	157	47.1 %	24	50.0 %	**49**	**39.2 %**	**29**	**48.3 %**	
BMI score			28.13 (6.52)		28.07 (7.67)		**28.41 (6.37)**		**28.03 (7.13)**	**0.843**
Long-standing conditions (LSC)	Yes	309	92.8 %	41	85.4 %	**11**	**89.6 %**	**53**	**88.3 %**	**0.173**
	No	19	5.7 %	6	12.5 %	**12**	**9.6 %**	**5**	**8.3 %**	
	Unknown	5	1.5 %	1	2.1 %	**1**	**0.8 %**	**2**	**3.3 %**	
LSC conditions	(n)		3.12 (1.83)		2.40 (1.44)		**2.99 (1.85)**		**3.03 (1.59)**	**0.057**
LSC conditions	0-3	195	58.6 %	40	83.3 %	**82**	**65.6 %**	**35**	**58.3 %**	**0.003**
	> 3	133	39.9 %	7	14.6 %	**42**	**33.6 %**	**23**	**38.3 %**	
	Unknown	5	1.5 %	1	2.1 %	**1**	**0.8 %**	**2**	**3.3 %**	
Alcohol consumption	Days last w.		1.75 (2.69)		1.87 (2.24)		**1.49 (3.22)**		**2.02 (2.40)**	**0.512**
	Units last w.		7.52 (15.33)		8.57 (12.62)		**5.89 (14.55)**		**9.39 (19.88)**	**0.491**

* Significance test for the Treatment group x Responder interaction. Group: "Offer" and "No offer" group. Responder: Patients with and without response to 6 month questionnaire. Interaction: Treatment group ("Offer" group = 1, "No offer" group = 0) x Responder (patients with 6 month response = 1, patients without 6 month response = 0)

Table 15. Randomised controlled trial: Baseline medication/treatment offer/no offer group, responders/non-resp. at 6 months

		Treatment arm								
		No offer group				Offer group				
		Response at 6 months		No response at 6 months		Response at 6 months		No response at 6 months		
Variable		**n**	**Mean (SD) %**	**n**	**Mean (SD) %**	**n**	**Mean (SD) %**	**n**	**Mean (SD) %**	**p-value***
Antidepressant use (current)	Yes	139	41.7 %	16	33.3 %	**56**	**44.8 %**	**25**	**41.7 %**	**0.009**
	No	0	0.0 %	1	2.1 %	**0**	**0.0 %**	**0**	**0.0 %**	
	Unknown	194	58.3 %	31	64.6 %	**69**	**55.2 %**	**35**	**58.3 %**	
Antidepressant use (past)	Yes	210	63.1 %	24	50.0 %	**78**	**62.4 %**	**25**	**41.7 %**	**0.671**
	No	103	30.9 %	21	43.8 %	**36**	**28.8 %**	**17**	**28.3 %**	
	Unknown	20	6.0 %	3	6.3 %	**11**	**8.8 %**	**18**	**30.0 %**	
Medication (all types)			4.89 (3.86)		2.91 (3.47)		**4.70 (4.00)**		**3.91 (3.51)**	**0.094**

* Significance test for the Treatment group x Responder interaction. Group: "Offer" and "No offer" group. Responder: Patients with and without response to 6 month questionnaire.

Interaction: Treatment group ("Offer" group = 1, "No offer" group = 0) x Responder (patients with 6 month response = 1, patients without 6 month response = 0)

There were significant differences in reported current use of antidepressants (p=0.009), but this difference was due to differences in response rates to the two questions posed to assess use of these medicines, and not in reported use or non-use of antidepressants. Non-responders at 6 months in the "No offer" group were more likely not to have responded to the question on current antidepressant use at baseline, whereas the other three groups were comparable (details in table 15).

The main identified differences in baseline characteristics was that non-responders at 6 months in the "No offer" group were more likely to be younger (10 year difference), employed and to live in more deprived areas; and less likely to have more than three long-standing conditions. Non-responders in the "Offer" group were less likely to be employed at baseline. A comparison of differences may be found in table 16 (Baseline differences between the offer and no offer group responders and non-responders at 6 months). Potential implications of between group differences are considered in the following paragraphs.

Table 16. Baseline differences between the offer and no offer group responders and non-responders at 6 months

No offer group		Offer group	
6 month responder	**6 month non-responder**	**6 month responder**	**6 month non-responder**
	More likely to be employed		Less likely to be employed
	More likely to be deprived		
	Lower age		
	Less likely to have > 3 LSC*		
	Less likely to have reported whether currently using ADs		

Characteristics with between-group differences at $p \leq 0.05$ are presented in the table. * LSC: Long-standing conditions

Regressing age on changes in depression scores

As the "No offer" group non-responders at 6 months on average were 10 years younger than the other three groups, a test was carried out to consider the effect of age on changes in depression scores from baseline to 6 months. Results of the analysis showed a change in mean change in PHQ-9 score of -0.008 (SE 0.019) per year of age (p=0.671). This result added up to a maximum difference of -0.080 in PHQ-9 scores over a 10 year period (< 3 ‰ difference for the PHQ-9 scale which ranges from 0-27 points) in "No offer" group non-responders at 6 months. This difference was so small that it seemed reasonable to ignore its influence and perform analyses without adjusting for age.

Conclusions about the risk of known potential confounding factors

In conclusion, no evidence was found to suggest there were significant differences in depression and anxiety outcomes at baseline when comparing "Offer" and "No offer" group responders and non-responders at 6 months. The same was true for most other baseline characteristics. Although between group differences were identified in a limited number of areas (employment status, deprivation score, age, the existence of more than three long-standing conditions, and the proportion of patients reporting whether they were currently using antidepressants or not), these were mostly differences between the "No offer" group non-responders at 6 months compared to the other three groups, and not "Offer" group non-responders. Apart from the fact that non-responders in the "Offer"

group were less likely to be employed at baseline, there were no statistically significant differences between "Offer" group non-responders (who had the lowest response rate to the 6 month questionnaire) and responders in both the "Offer" and "No offer" group.

Overall, the identified differences in five out of 20 baseline covariates, of which none were depression and anxiety outcome measures, appeared to be unlikely to influence outcomes at 6 months. Therefore it was reasonable to assume that between group comparisons of outcomes at 6 months could be carried out with limited risk of significant influence of any known potential confounding factors.

5.8 The treatment provided by homeopaths for depressed patients

The first 6 months of the trial, the 74 patients who accepted the offer of treatment had a total of 278 consultations, with a median of 4 consultations per patient (interquartile range 3.0–5.0, range 1.0–7.0). The trial period started from random selection, whereas the first consultations took place 2 – 3 months later. The median treatment period was therefore 3.3 months (IQR 2.5–3.9).

Homeopathic treatment was tailored to suit the individual patient's needs and was practised according to the practitioners' treatment style. The prescribed homeopathic remedy was individualised to each patient, which meant that ten different patients with the same medical condition could all be prescribed different homeopathic remedies. Moreover, length and frequency of consultations, and any additional advice given, could be tailored to suit the needs of the patient and according to the treatment style of the practitioner. Median duration of consultations in the trial was 60 minutes (IQR 53–69), with 90 minutes (85–110) spent on the first consultation and 45 minutes (37–57) for follow-up sessions.

Prescription of homeopathic remedies

Out of a total of 48 different homeopathic remedies, the six most commonly used remedies (Natrium muriaticum, Ignatia amara, Carcionisinum, Aurum metallicum, Sepia succus and Lycopodium clavatum) covered more than half of all 275 prescriptions (table 18: Homeopathic remedies prescribed by practitioners – data for first 6 months). Thirty-five

different remedies (72.9%) were only prescribed one to four times each, and collectively covered one quarter of all prescriptions. The remaining seven remedies were given to patients from five to 10 times. Remedies were prescribed in 14 different potencies (dilutions), most commonly in 30C (23.3%), 200C (18.9%) potencies and LM1 (14.2%).

Table 18. Homeopathic remedies prescribed by practitioners – data for first 6 months

Prescriptions	N=275 (100%)	Each remedy
Nat-m	43 (15.6 %)	43 (15.6 %)
Ign	27 (9.8 %)	27 (9.8 %)
Carc	23 (8.4 %)	23 (8.4 %)
Aur	21 (7.6 %)	21 (7.6 %)
Sep	20 (7.3 %)	20 (7.3 %)
Lyc	11 (4.0 %)	11 (4.0 %)
Arg-n	10 (3.6 %)	10 (3.6 %)
Staph	9 (3.3 %)	9 (3.3 %)
Ars	8 (2.9 %)	8 (2.9 %)
Puls, Sulph	14 (5.1 %)	7 (2.5 %)
Calc	6 (2.2 %)	6 (2.2 %)
Arn	5 (1.8 %)	5 (1.8 %)
Helx, Plb, Tub	12 (4.4 %)	4 (1.5 %)
Several (n=8) *	24 (8.7 %)	3 (1.1 %)
Several (n=10) **	20 (7.3 %)	2 (0.7 %)
Several (n=14) ***	14 (5.1 %)	1 (0.4 %)
Unknown	8 (2.9 %)	8 (2.9 %)

Potencies	N=275 (100 %)
30C	64 (23.3 %)
200C	52 (18.9 %)
LM1	39 (14.2 %)
1M	33 (12.0 %)
LM2	27 (9.8 %)
6C	15 (5.5 %)
12C	13 (4.7 %)
LM3	12 (4.4 %)
7C	6 (2.2 %)
LM4	3 (1.1 %)
10M	3 (1.1 %)
6X	2 (0.7 %)
15C	2 (0.7 %)
LM5	1 (0.4 %)
Unknown	3 (1.1 %)

Only abbreviations for homeopathic remedies are presented in the table.
*3 prescriptions (1.1 %) for each of the following remedies: Acon, Bufo, Kali-bi, Kali-c, Lac-c, Lac-equi, Phos, Stram
** 2 prescriptions (0.9 %) for each of: Bar-c, Calc-p, Carb-v, Dig, Foll, Lil-t, Mixed grass, Nux-v, Plat, Spong
*** 1 prescriptions (0.4 %) for each of: Aur-m-n, Calend, Caust, Coff, Euphr, Gels, Lac-lup, Lach, Luna, Passiflora, Psor, Rhod-met, Rhus-t, Syph

Other advice given to patients

Homeopaths offered patients additional advice at 63 (22.7%) of the 278 consultations. Most commonly they recommended changes to patients' diet (36.5% of the advice, 8.3% of all consultations). This involved drinking more water in half of the cases, but also reducing intake of sweets, fats, caffeine and alcohol, and increasing fruits, vegetables and fibre in the diet. Almost one quarter of the advice (23.8%) involved "referral" to other practitioners (5.4% of all consultations), primarily to patients' GPs, but also to seek mental health support from psychotherapists or other "talking therapy" consultants, and less commonly to other CAM practitioners (n=2). Almost as common (22.2% of the advice, 5.0% of all consultations) were recommendations for various forms of self-care, such as relaxation and stress management techniques, improved management of everyday life

activities to reduce stress, and increased social activities. The remaining 17.5 % of the advice (4.0% of all consultations) consisted of various forms of supplements, herbal teas, Bach flower remedies (Ernst 2010a) and other products that could be bought over the counter. No homeopath reported recommending the use of St. John's Wort (Hypericum), a commonly use herb used for depressive symptoms (Linde et al. 2008).

Comparison of the practice of the seven homeopaths

The seven homeopaths providing the intervention treated different numbers of patients, ranging from 6 to 15 (table 17). The two main reasons for this were differing numbers of patients recruited to the trial in each of the geographical areas where homeopaths provided treatment, and varying degrees of homeopaths' availability. The median length of consultations varied from practitioner to practitioner (38–69 minutes), with considerable differences for both the first (60–120 minutes) and follow-up (30–57 minutes) consultations.

The median number of homeopathic remedies prescribed for individual patients also varied from homeopath to homeopath (1–5 remedies), even though differences in the median treatment period were not as considerable (3.1–3.7 months). Hence, some homeopaths prescribed homeopathic remedies more frequently than others.

Homeopaths had been asked at each consultation to indicate the degree to which they felt confident about their prescription of homeopathic remedies on a 0 to 10 point scale (0=not confident at all, 10=entirely confident). The median degree of confidence in prescriptions varied between different homeopaths, ranging from 6.1 to 9.5 (median for all patients 8.3). Practitioners were also asked to consider to what extent they expected their patients' two main complaints to improve over the entire treatment period. The median expected improvement ranged from 19 % in one homeopath to 80 % in another, with a median expectation of 50 % for all homeopaths. Homeopaths' expectations in patients improvement were significantly correlated to their confidence in their prescriptions ($p<0.001$).

Table 17. Treatment provided by homeopaths – data for first 6 months of the trial

Practitioners	**P1***	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**All**
Patients (n)	15	6	8	14	10	15	6	**74**
Consultations (n) (sum)	60	22	28	47	51	48	22	**278**
Consultations (median) (IQR)	4.0 (4.0–4.0)	4.0 (3.0–4.0)	4.0 (2.0–5.0)	3.0 (3.0–4.0)	5.0 (4.0–6.0)	4.0 (2.5–6.0)	4.0 (3.0–5.0)	**4.0 (3.0-5.0)**
Treatment period (months)	3.3 (3.2–4.2)	2.8 (2.8–2.9)	3.7 (1.3–4.1)	3.6 (2.8–4.2)	3.1 (1.4–3.3)	3.3 (1.2–3.4)	3.3 (2.9–4.1)	**3.3 (2.5-3.9)**
Consultation length (minutes)**								
First consultation	120 (100–120)	60 (60–60)	75 (60–90)	105 (90–120)	90 (80–105)	90 (90–90)	90 (90–100)	**90 (85-110)**
Follow-up consultations	45 (38–51)	30 (30–30)	40 (33–53)	57 (44–59)	49 (43–53)	48 (43–60)	41 (39–45)	**45 (37-57)**
All consultations	61 (56–66)	38 (38–40)	55 (43–67)	69 (62–75)	58 (54–62)	63 (56–73)	56 (53–58)	**60 (53-69)**
Remedies (n) (sum)	67	32	27	50	49	25	25	**275**
Remedies (median) (IQR)	5.0 (4.0–5.0)	5.0 (5.0–6.0)	4.0 (1.5–5.0)	3.5 (2.0–5.0)	5.0 (4.0–6.0)	1.0 (1.0–2.0)	5.0 (3.0–5.0)	**4.0 (2.0-5.0)**
Confidence in prescription ***	8.6 (8.0–9.5)	9.2 (9.1–9.2)	8.6 (8.4–8.8)	6.1 (5.4–6.9)	6.6 (5.4–7.3)	9.5 (9.4–9.8)	7.7 (7.6–7.9)	**8.3 (6.6-9.3)**
Other advice (n) (sum, percent) #	7 (11.7 %)	3 (13.6 %)	15 (53.6 %)	8 (17.0 %)	16 (31.4 %)	14 (29.2 %)	0 (0.0 %)	**63 (21.8 %)**
Expectation improvement (%) ##	75 (50–93)	78 (50 –85)	48 (33–53)	23 (20–38)	19 (3–35)	80 (73–85)	30 (25–35)	**50 (35 –80)**

Median & interquartile range (IQR) (25th and 75th percentile using Tukey's Hinges). * P1: Practitioner 1, P2: Pract. 2, etc. ** 1st: 1st consultation. FU: Follow-up consult. All: 1st & follow-up consult. *** Practitioners rating of confidence in prescription of hom. remedies, data collected for each consult. on 0–10 point VAS scale. # Other advice: N consultations where hom. gave advice in addition to or instead of hom. remedies, % of consult. ## Pract. rated (%)degree to which they expected patients complaints would improve. N consult. where advice was given and % of N of consult. for individual hom. and for consult. overall. NA: Practitioner provided insufficient data to assess rating of expectations of improvement.

There was considerable variation in the frequency with which homeopaths provided additional advice alongside homeopathic treatment, ranging from no recommendations at all to recommendations made at more than half of the consultations.

Summary of treatment data

Seventy-four patients had 278 consultations over the first six months of the trial (median 4 consultations), but treatment first started 2 – 3 months after random selection so the median treatment period was 3.3 months. First consultations lasted about 90 minutes and follow-up consultations 45 minutes. Forty-eight different homeopathic remedies were prescribed in 14 different potencies (dilutions), with 73 % prescribed only 1 – 4 times throughout the treatment period. Homeopaths offered additional advice to patients in almost one quarter of the consultations. There were considerable variations in consultation

length, number of remedies prescribed and advice received between patients, and there were significant differences in treatment styles between homeopaths.

5.9 Safety of treatment provided by homeopaths for depressed patients

The safety of treatment provided by homeopaths for depressed patients was assessed by considering the number and nature of adverse events and risk reports submitted by homeopaths, patients, their clinicians, a psychotherapist, and through information obtained during qualitative interviews. In addition, questionnaire responses from all patients, including those in the "Offer" and the "No offer" group, were used to assess any potential risk of self-harm. Categorisation of adverse events was done using the WHO-UMC system for assessment of causality (WHO-UMC undated) and the severity of adverse events was assessed using the CTCAE guidelines (NIH/NCI 2010). Details of the WHO-UMC and the CTCAE guidelines are presented under Table 19 (Adverse events in patients treated by homeopaths during the trial). In brief, the WHO-UMC guidelines were used to consider whether the product assessed was assumed to be certain, probable/likely, possible or unlikely to have caused the adverse event, or whether it may be unclassified or not assessable (due to insufficient available information). The CTCAE guidelines were used to classify the severity of adverse events, using the categories mild, moderate, severe, life-threatening and death (details in table 19). Adverse events could be considered to be serious if they resulted in severe adverse events with hospitalisation or prolonged hospitalisation, or disability or limited ability for self-care; if they were life-threatening; or if they resulted in death.

Procedures put into place to assess the safety of patients treated by homeopaths

The trial protocol contained guidelines to ensure the safety of patients. The sponsor was the University of Sheffield, thereby holding insurance against liabilities arising out of the research project. An assessment was therefore carried out by the University of Sheffield prior to start of the trial. The project was categorised as having potentially medium risk. Therefore, The Health & Human-Interventional Studies Research Governance Committee at the University of Sheffield met with the researchers to check that quality control systems were put into place in order to safeguard the dignity, rights, safety and wellbeing of

patients. A report may be found in Appendix 17 (Health & Human-Interventional Studies Research Governance Committee, Report on the visit to ScHARR to discuss the DEPSY clinical trial).

Table 19. Adverse events in patients treated by homeopaths during the trial

AE	Patient	Report	Event reported	Duration	Time since* hom.*	Severity **	Causality***	Note
1	1	R1	As painless burn under lip after hom. remedy	1 day	Immediate	1	Probable/likely	No reaction when remedy was put under tongue
2	2	H5	Bad odour and taste of homeopathic remedy	Short	Immediate	1	Certain	Confirmed by homeopath, Rx past expiry date
3	3	R1	Headache	Short	Short	1	Probable/likely	Return on re-challenge, not after reduction of dosage
4	4	R1	Slight headache	1-2 minutes	30 minutes	1	Probable/likely	Symptom returns (after 30 min) on re-challenge
5	5	R1	Pressure forehead, fear intensified	Short	Short	1	Probable/likely	Returns on re-challenge, followed by improvement
6	6	R1	Easy bruising	Unclear	Unclear	1	Unclassified	Return of old symptom (4 years earlier)
7	7	R1	Irritability/mood swings	A few days	Short	1	Possible	
8	2	H5	Pain and cramping in back	Transient	3 & 4 days	1	Possible	
9	8	R1	Tiredness, light headed, strange feeling	1 day	Immediate	1	Probable/likely	
10	9	H1/R1	Weeping, dizzy, nausea, no appetite, indecisive	10 min-2 days	1 day	1	Probable/likely	Followed by improvement
11	10	H1	Chest pain	15 min	8 days	1	Possible	Hospital exam negative
12	11	H4/R1	Severe pain in chest, back, neck, jaw	Transient	A few days	3	Possible	Medical exam negative, possible cause: stress
13	11	H4/R1	Severe headache	A few hours	A few days	3	Possible	Hospital exam negative, possible cause: stress
14	12	R1	Chronic pain aggravated, felt dreadful	Three weeks	A few days	2	Possible	Possible infection, antibiotics no effect, rechallenge neg
15	13	H2	Death due to sepsis and multi-organ failure	NA	Treated for 9 months	5	Unlikely	Long-standing chronic conditions: morbidly obese (BMI > 50), diabetes with leg ulcers and high blood pressure, followed up by hospital, GP, nurse and dietitian
16	14	H1	Sickness, diarrhoea	1-2 days	3 days	3	Unlikely	Preceded by 3 day constipation, hospitalised, surgery for hernia due
17	10	H1	Flu-like symptoms	8 days	3 weeks	1	Unlikely	GP exam: slight chest infection, antibiotics
18	15	H6	Loss of memory, weeping	Unclear	3 months	1	Unlikely	Possible cause: Bereavement
19	16	H6	Self-harming aggravated	2 days	5 day course	1	Unlikely	Possible cause: Bereavement
20	17	H6	Anxiety	Unclear	2 weeks	1	Unlikely	Possible cause: Bereavement, handled better after hom.
21	18	H6	Worry, frustration, tiredness	Transient	4 weeks	1	Unlikely	Possible cause: Stress
22	19	H6	Upset, worried, devastated,	Unclear	2 weeks	1	Unlikely	Possible cause: Stress
23	20	H3	Worry	Transient	A few days	1	Unlikely	Worry was about an upcoming surgery
24	21	R1	Vomiting	Transient	Short	1	Probable/likely	Return on re-challenge

H: Homeopath (number refers to specific homeopath). R1: Researcher (qualitative interview).
* Time since took homeopathic remedy.
** Severity grade, according to Common Terminology Criteria for Adverse Events (CTCAE) (NIH/NCI 2010) – further details below.
*** Categories of adverse events according to WHO-UMC guidelines – further details below.

** Severity grade according to Common Terminology Criteria for Adverse Events (CTCAE):
Grade 1: **Mild**. Mild symptoms or clinical/diagnostic observations; or there is no indication for an intervention.
Grade 2: **Moderate**. Minimal, local or non-invasive intervention or limitations or limitation in activities of daily living such as eating, shopping, using a phone, managing money
Grade 3: **Severe**. Severe or medically significant but not immediately life-threatening, or hospitalisation/prolongation of hospitalisation, disabling event, or limitation in activities of daily living such as bathing, dressing/undressing, eating, using the toilet, taking medications, and the patient is not bedridden, or congenital anomaly or birth defect, or event requires intervention to prevent any of the mentioned consequences.
Grade 4: **Life-threatening**. Life-threatening consequences or urgent intervention indicated due to risk of death.
Grade 5: **Death** related to AE.

National Institutes of Health (NIH) and National Cancer Institute (NCI), U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Published: May 28, 2009 (v.403: June 14, 2010). Available at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (last visited 09.05.2015)

*** Categories of adverse events according to WHO-UMC guidelines:

Certain:
- Event or laboratory test abnormality, with plausible time relationship to drug intake;
- Cannot be explained by disease or other drugs, response to withdrawal plausible (pharmacologically, pathologically);
- Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) (if this category is not fulfilled, then even if re-challenge observation is positive, the case cannot qualify as Certain);
- Re-challenge satisfactory, if necessary (this category is required, unless the evidence in the report is sufficiently convincing without it).

Probable/Likely:
- Event or laboratory test abnormality, with reasonable time relationship to drug intake;
- Unlikely to be attributed to disease or other drugs;
- Response to withdrawal clinically reasonable;
- Re-challenge not required.

Possible:
- Drug causality is one of other possible causes;
- Event or laboratory test abnormality, with reasonable time relationship to drug intake;
- Could also be explained by disease or other drugs;
- Information on drug withdrawal may be lacking or unclear.

Unlikely:
- Exclusion of drug causality seems most plausible;
- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible),
- Disease or other drugs provide plausible explanations.

Conditional/Unclassified:
- Event or laboratory test abnormality;
- More data for proper assessment needed or additional data under examination.

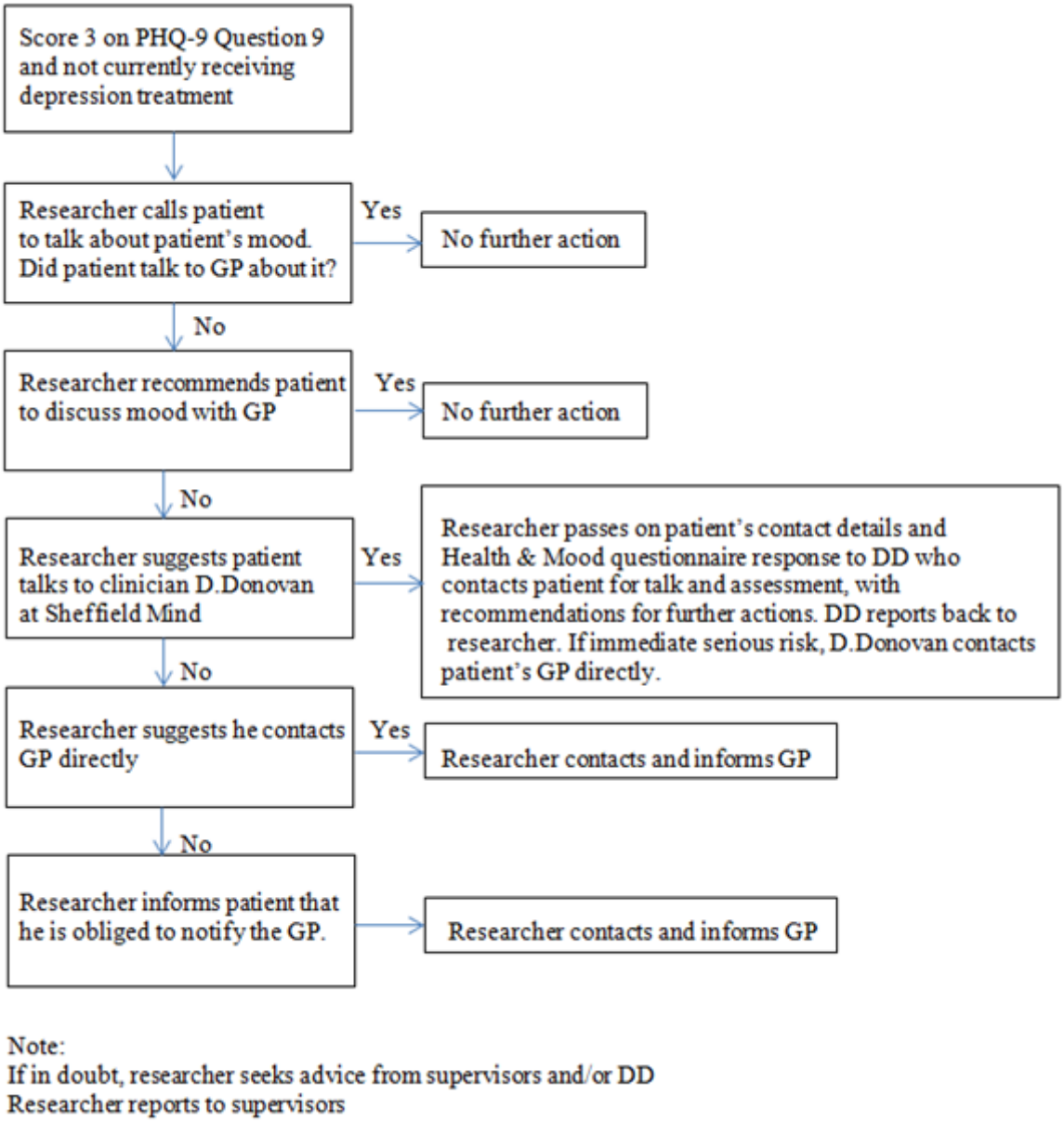
Unassessable/Unclassifiable:
- Report suggesting an adverse reaction;
- Cannot be judged because information is insufficient or contradictory;
- Data cannot be supplemented or verified.

World Health Organization and Uppsala Monitoring Centre. The use of the WHO–UMC system for standardised case causality assessment. [Online] Available from: http://www.WHO-UMC.org/graphics/4409.pdf (Accessed 08.04.2015)

The trial Steering Committee ratified the research protocol and procedures, including the safety measures. Risk assessment guidelines were developed in cooperation with the Steering Committee and a psychotherapist at Sheffield Mind, an independent charity providing services to support people with mental health problems. Sheffield Mind had a

consultative, educative and advisory role in this project, and support was provided by senior psychotherapist Debra Donovan. A risk assessment flow chart may be found in Figure 10 (Flow chart for dealing with potential risk of self-harm for the DEPSY trial 140101). Results may be found in section 5.9.2 (Potential risk issues).

Figure 10. Flow chart for dealing with potential risk of self-harm for the DEPSY trial



In the information sheet sent to those offered treatment, patients were asked to contact the researchers if they had concerns or experienced any negative effects following treatment. Complaints could also be filed directly to the University of Sheffield without contacting the

researchers. Patients consented to continuing standard medication as prescribed by their GP/specialist and they were informed that their homeopath would contact their GP if needed. Out of 74 patients treated by homeopaths, 29 reported on their baseline Mood and Health Questionnaire that they were taking antidepressants. One patient reported at 6 months no longer taking antidepressants, six did not respond to this question, and the remaining 22 patients were still taking antidepressants. It is unclear whether the patient who stopped using antidepressants had done so by her own decision or whether this was in agreement with her GP.

All homeopaths had liability insurance and were bound by their professional association's Code of Ethics and Practice, and were also obliged to report any adverse events and risk issues to the researchers. Guidelines and procedures, as described in the methods chapter, were developed prior to study start in order to support homeopaths in identifying and reporting any arising adverse events or risk issues. Homeopaths and researchers underwent safety training provided by Sheffield Mind and safety issues were also addressed at six out of eight meetings that the researchers arranged for homeopaths.

5.9.1 Reports of adverse events following treatment by homeopaths

A total of 24 adverse events in 21 patients (28.4% of all patients treated by homeopaths) were reported during the research project. Twelve adverse events occurring in 10 patients were reported by homeopaths, nine were identified during qualitative interviews, and three events (two patients) were found through both sources. Hence, adverse events were more likely to be reported by the researcher than the homeopaths (homeopaths 16.2% of 74 treated patients, researcher 33.3% of 33 interviewed patients). This was in part due to the guidelines stating homeopaths should only report serious adverse events. For adverse events categorised by the researchers as certain, probable/likely or possible to be related to the treatment, differences were even more considerable (homeopaths n=4, 5.4%; researcher n=10, 30.3%) (adverse events in two patients were reported by both). No reports were received from patients' GPs or other healthcare practitioners. Details of all adverse events may be found in table 19 (Adverse events in patients treated by homeopaths during the trial).

Two researchers (PV and PF, both homeopaths with knowledge of the effects of homeopathic remedies) independently of each other assessed each report. Probable causality between the intervention and the adverse events was determined by using the WHO-UMC guidelines, and the severity of each adverse event by using the CTCAE guidelines (NIH/NCI 2010). For 19 out of 24 adverse events the two researchers' assessment of probable causality corresponded and in 21 out of 24 cases the severity of adverse events corresponded. For reports where the researchers' initial assessments did not correspond, additional information on each event was provided and cases were discussed between the two researchers, who reached consensus on the interpretation of all reported adverse events.

Causality of adverse events

Using the WHO-UMC guidelines, 14 out of 24 adverse events, reported by 12 patients, were considered to be either ***certain*** (n=1), ***probable or likely*** (n=7), or ***possible*** (n=6) to have been caused by homeopathic treatment, whereas in 10 cases causality was ***unlikely*** (n=9) or ***unclassified*** (n=1) (table 19: Adverse events in patients treated by homeopaths during the trial).

Adverse events certain, probable/likely or possible to be caused by the intervention

The 14 adverse events considered to be at least possibly related to the intervention were categorised as ***mild*** (n=11), ***moderate*** (n=1) and ***severe*** (n=2).

The only adverse event categorised as ***certain*** to have been caused by homeopathic treatment was a bad odour and taste of a homeopathic remedy. It was reported by the patient directly to the homeopath, who also confirmed the bad odour. The remedy was sent to the manufacturer (Helios Homeopathic Pharmacy) for assessment. The manufacturer concluded that the taste and odour was likely to have been caused by an interaction between the alcohol solution and the plastic container used to preserve the homeopathic remedy and it had been stored past its expiry date, possibly resulting in bi-products (aromatic ethers). All homeopaths were consequently reminded by the researcher to be aware of expiry dates to ensure all homeopathic remedies were safe for patients to take. The event was categorised as ***mild*** as the patient did not report any symptoms following the medication.

Seven adverse events were considered ***probable or likely*** to be caused by the intervention. All were considered to be ***mild*** and lasted a short period of time, for up to one day. Three of these patients reported headache, with one also experiencing an intensification of fear. One patient complained of becoming tired and lightheaded. Another vomited after taking a homeopathic remedy and one patient felt nauseated, dizzy, experienced loss of appetite and was weeping and indecisive. The last patient had a painless sensation of a burn under her lip, lasting for one day, after the homeopathic remedy got stuck there, instead of under the tongue. The patient who vomited after taking the homeopathic remedy and three patients who experienced headache, reported return of symptoms shortly after each time they took the homeopathic remedy, thereby fulfilling the re-challenge criterion in the WHO-UMC guidelines. In one of these patients symptoms no longer occurred when the amount of the homeopathic remedy was reduced from three drops to one drop daily. Two of the patients reported a significant improvement in their mood and state of health shortly after each adverse event. Such a reaction corresponds to what homeopaths refer to as a "homeopathic aggravation", which is considered to be a sign of the body's healing processes (Stub et al. 2012).

In the six cases where causality was considered to be ***possible***, most symptoms appeared within a few days, but in one case immediately after taking the homeopathic remedy and in another only after eight days. One patient reported ***severe*** headache and at another time ***severe*** pain in chest, back, neck and jaw. These events were categorised as ***severe***, based on the patient's description of the pain, but all symptoms were transient and medical exams did not reveal any pathology. Transient chest pain, occurring eight days after taking the homeopathic remedy, was also reported by another patient, but was categorised as ***mild***. As in the other patient reporting chest pain, hospital exams were negative. Another patient, who experienced an intensification of his chronic pain condition for about 3 weeks, was considered by the GP to possibly have an infection, although no improvement followed the use of antibiotics. The severity of the event was categorised as ***moderate*** as he reported "feeling dreadful". He did not experience return on these symptoms on repeating the homeopathic remedy. The remaining two patients experienced pain and cramping in back and irritability and mood swings, both considered to be ***mild*** adverse events.

Adverse events unclassified or unlikely to be caused by the intervention

The 10 adverse events considered to be ***unclassified*** (n=1) or ***unlikely*** (n=9) to be related to the intervention, included one ***death***, a ***severe*** adverse event, and eight ***mild*** events. All events categorised as ***unlikely*** had other plausible causes of symptoms, none fulfilled the criterion of return of symptoms on re-challenge, and in five events symptoms appeared relatively long after taking the homeopathic remedy (from 2 weeks to 3 months).

During the course of the trial, one of the homeopaths reported that one of the patients died. The patient aged 55 had, according to his wife, died from sepsis and multi-organ failure. He had multiple long-standing chronic conditions since before joining the research project. The patient was morbidly obese (BMI > 50) and had diabetes with leg ulcers and high blood pressure. Prior to and during the trial the patient was followed up by his GP, nurse and dietitian on a weekly or monthly basis, and during the trial also by the hospital every 2 weeks. He reported taking several types of conventional drugs before and during the trial, for diabetes (including insulin injections), medication for hypertension, diuretics for oedema and congestive heart failure, as well as statins. The ***death*** of this patient was considered to be ***unlikely*** to be related to the intervention.

The event categorised as ***severe*** and ***unlikely*** to be caused by the intervention, involved diarrhoea caused by a hernia, for which the patient had surgery. The patient first suffered from constipation for 3 days, then took the homeopathic remedy and following this, had diarrhoea. Upon hospital exam a hernia was identified as the cause of the symptoms. The hernia is likely to have resulted from weakness of the abdominal wall due to former cholecystectomy.

A single report of a ***mild*** adverse event was considered to be ***unclassified*** as there was insufficient information to determine the duration of the event and the time period from when the patient took the homeopathic remedy to when the symptom first occurred.

In summary, adverse events were reported by 28.4 % of all patients treated by homeopaths. Fourteen adverse events in 12 patients (16.2% of all patients treated by homeopaths) were categorised by the researchers to be ***certain***, ***probable/likely*** or ***possible*** to have been caused by homeopathic treatment. None of these were life-threatening events and all were

transient. Adverse events were more likely to be reported by the researcher than the homeopaths.

5.9.2 Potential risk issues

Potential risk was in the risk guidelines developed for the trial defined as risk of suicide, significant self-harm, being harmed by or causing harm to others, or significant deterioration in a person's mental health. A total of 58 patients (10.2%) were considered to be at potential risk, of which 36 were in the "No offer" group (9.4% of 381 patients) and 22 were in the "Offer" group (11.9% of 185 patients).

Risk was mostly identified through the mood and health questionnaire (n=55), with 54 patients indicating they had thoughts nearly every day of being better off dead or of hurting themselves (question 9 in PHQ-9) and currently not taking antidepressants, and one patient had made a handwritten remark asking for help. The remaining three patients were identified by homeopaths (n=2) and the researcher during a qualitative interview (n=1). Question 9 in PHQ-9 has been found to be a useful to predict suicide attempts (Simon et al. 2013).

No action was taken for seven patients who had indicated on their questionnaires that they had recently been followed up by their GP. Seventeen out of the remaining 51 trial participants who were considered to be at potential risk were contacted by the researcher (PV) by telephone, whereas letters were sent to 34 of patients' GPs, where patients could not be reached by telephone or email (n=26) or no such contact details were available (n=8).

Out of the 17 patients who were reached by telephone, nine had already discussed their mood with their GP. One of these patients had been offered antidepressants by his GP, but refused to take them. This patient was assessed by the senior psychotherapist at Sheffield Mind (DD), who found no current risk. The researcher (PV) sent a letter to the patient's GP to inform about this patient. Five of the 17 patients who were reached by telephone agreed to discuss their mood with their GP. One of these patients had been offered antidepressants by the GP, but did not find these were sufficiently helpful and was therefore assessed by the

psychotherapist and offered support by Sheffield Mind. The remaining three patients were also assessed by the psychotherapist. Two of these patients were not found to be at risk and the last patient was interviewed by the researcher (PV) shortly after. This patient was then found to have improved considerably, with no current risk involved. The Steering Committee Chair (Simon Gilbody) was consulted by the researcher (PV) regarding one of the 17 patients for a second opinion, and the Chair agreed with the assessment.

It is not known that any serious adverse events were caused by any of the identified incidents.

In summary, potential incidents of risk issues were identified in 10.2 % of the patients included in the trial. The majority of these reports were identified through the questionnaires sent to patients. No serious adverse events were reported to result from these incidents.

5.10 Depression at 6 months: Intention-to-treat analyses

An intention-to-treat analysis (ITT-analysis) was carried out to compare depression (PHQ-9) and anxiety (GAD-7) outcomes in the "Offer" and "No offer" groups. For the ITT-analysis, patients remained in the group they were randomly selected to, irrespective of whether "Offer" group patients received treatment by a homeopath or not.

Two analytic approaches were carried out to assess depression (PHQ-9) (primary outcome) and anxiety (GAD-7) (secondary outcome) scores at 6 months, a general linear model (GLM) and a generalised estimating equations (GEE) method, both taking into account baseline covariates.

Analyses of results were carried out with no imputation for missing data (and calculation of PHQ-9 sum scores also for patients who did not respond to all questions), and with imputation of missing data using three approaches: Multiple Imputation (MI), Last Observation Carried Forward (LOCF) and Regression Imputation (RI). The main results reported are based on Multiple Imputation for missing data.

The appropriateness of carrying out Multiple Imputation for missing data

The frequency and pattern of missing data for the two outcome measures at baseline and 6 months was assessed. PHQ-9 consists of nine and GAD-7 of seven questions. The frequency of missing data for PHQ-9 questions at baseline was considered to be low (1.4%), ranging from 0.2 % for question 2 (feeling down, depressed or hopeless) to 2.4 % for question 5 (poor appetite or overeating) and somewhat higher at 6 months (mean 4.0%, range 0.4% – 5.7%), and for GAD-7 at baseline (mean 3.7%, range 2.4% – 5.5%) and 6 months (mean 5.8%, range 4.2% – 8.3%). In summary, the proportion of missing values was considered to be reasonably low. Little's MCAR test (Little 1988) was carried out in order to try to determine if there was any systematic pattern in missing data. Significance tests showed that neither PHQ-9 at baseline ($p=0.118$) or 6 months ($p=0.407$), nor GAD-7 ($p=0.484$, $p=0.996$) were below the 0.05 threshold level.

In summary, it seemed reasonable to assume there was no pattern in missing data, and Multiple Imputation for missing values could be carried out.

The influence of baseline covariates on PHQ-9 scores at 6 months

In order to determine which baseline covariates to include for assessing 6 month outcomes using a marginal general linear model and regression imputation, the influence of baseline covariates was assessed. A hierarchical model was applied.

The line of reasoning for the hierarchical model is here briefly described. Some research suggests that depression outcomes may be influenced by covariates such as anxiety (Choi et al. 2013, Nasso 2011, Papakostas & Larsen 2011), employment status (De Bolle 2010) and gender (Josephson et al. 2006, Schoenbaum et al. 2005). These covariates were taken into consideration when developing the hierarchical model. Since the trial intervention offered was treatment provided by homeopaths, the homeopaths were consulted to hear their opinion on which covariates might influence the main outcome to a greater or lesser extent. Independently of each other they were asked to rank covariates from "most likely" to influence the depression outcome measure, to "least likely". Five out of seven homeopaths responded. The collective results showed that they considered the baseline PHQ-9 score as the covariate most likely to affect 6 month depression scores, followed by the onset of depression, the use of antidepressants, other long-standing conditions, the

anxiety score, employment status, alcohol consumption, BMI score, gender and age (by omission the deprivation quintile was not asked about). In order to rank covariates according to their potential influence on depression outcomes, I took into account the literature, homeopaths' views, my own clinical experience and professional opinion, starting with the most important baseline covariate:

1) Depression (PHQ-9) score
2) Current antidepressant use
3) More than 3 long-standing conditions
4) Anxiety (GAD-7) scores
5) The first onset of depression
6) Employment status
7) BMI score
8) Alcohol units per week
9) Deprivation (IMD) quintile
10) Gender
11) Age

Multivariable linear regression models were assessed to evaluate the influence of covariates on the main outcome measure, PHQ-9 at 6 months. Any covariate with a p-value of 0.2 or less was included in the model. The approach used involved inclusion of the main outcome measure (PHQ-9 score at 6 months) as the dependent variable and all 11 mentioned covariates listed above as independent variables. Covariates were removed from the model one at the time, starting with the last one which gave a p-value above 0.2. New tests were run each time a single covariate was removed. The final model then included only those covariates which gave p-values of 0.2 or less. After all tests had been carried out, the following four covariates remained in the model (unstandardised coefficients with standard deviation and p-values reported):

1) Depression (PHQ-9) score: 0.741 (SD 0.061), p=0.000
2) Current antidepressant use (yes): 1.168 (SD 0.541), p=0.032
3) More than 3 long-standing conditions (yes): 0.918 (SD 0.570), p=0.108
4) Gender (female): -1.179 (SD 0.535), p=0.028

The model explained 31.7 % of the variance (R^2=0.317). The most significant contributor to the model was the baseline PHQ-9 score, which on its own contributed to 29.7 % of the variance (R^2=0.297).

Evidence of multicollinearity was also tested. This arises when several covariates are correlated (Field 2009). In such an event, two or more covariates overlap (Yoo et al. 2014). Such a situation can for example arise if two or more covariates are used to assess patients' degree of depression at baseline. The consequence is that standard errors (for beta coefficients) increase, resulting in wider confidence intervals. This reduces the probability that the coefficient is representative of the population. Moreover, if there is multicollinearity, then the second (and third) covariate(s) will add little to the model (little increase in the R^2 value). Multicollinearity should therefore as much as possible be avoided. Tolerance can be used to assess the relationship between covariates. The threshold level set by various authors ranges from 0.10 to 0.25 (Tabachnick & Fidell 2001, Menard 1995, Huber & Stephens 1993). Several researchers refer to Menard (Field 2009), who suggested the minimum should be 0.20 (Menard 1995). Any value below this could be problematic. Collinearity statistics carried out for the trial data identified tolerance levels ranging from 0.883 to 0.999. It was therefore assumed that any overlap between the four included covariates was unproblematic.

A histogram showed that the dependent variable (PHQ-9 at 6 months) had a normal distribution. A scatterplot showed homoscedasticity (residuals were spread out) and there seemed to be linearity of the model. A P-P Plot test of the regression standardised residual showed that the observed data were fairly similar to the expected data (they fell on the straight line). Results may be seen in figures 3, 4 and 5 (Histogram, Normal P-Plot of Regression Standardized Residual and Scatterplot for Regression Standardized Residual/Regression Standardized Predicted Value).

In conclusion, it seemed reasonable to apply the model including PHQ-9 baseline scores, the use of antidepressants, the existence of more than 3 long-standing conditions, and gender as covariates to assess 6 month outcomes using a marginal general linear model and general estimating equations, and for regression imputation.

5.10.1 Depression assessed at 6 months – primary analysis (ITT-analysis)

The primary ITT analysis was carried out using a General Linear Model (GLM) comparing depression measured on PHQ-9 at 6 months in the "Offer" and "No offer" group, controlling for baseline covariates, and using Multiple Imputation (MI) for missing values. Analyses using no imputation (and calculation of PHQ-9 sum scores also for patients who did not respond to all questions), Regression Imputation (RI) and Last Observation Carried Forward (LOCF) for missing values are also presented.

In summary, it seemed reasonable to assume there was no pattern in missing data, and Multiple Imputation for missing values could be carried out. Therefore it was reasonable to assume that between group comparisons of outcomes at 6 months could be carried out with limited risk of significant influence of any known potential confounding factors.

For all analyses two models were used, the primary model which controlled for baseline PHQ-9 measures alone, and the secondary also for baseline antidepressant use, the existence of more than three long-standing conditions and gender. Results are presented in table 20 (Depression outcomes at 6 months – Intention-to-treat analysis). In the main analysis "Offer" group patients reported 1.4 points lower depression (PHQ-9) scores at 6 months post-randomisation compared to "No offer" group patients (95% CI 0.2, 2.5, n=458, p=0.019), when controlling for baseline PHQ-9 scores and using MI for missing values.

Table 20. Depression outcomes at 6 months – Intention to treat analysis

Baseline covariates controlled for	PHQ-9 (n=458)			PHQ-9, AD, >3LSC, gender (n=451)		
	Mean (95% CI)*	p-value	Effect size**	Mean (95% CI)	p-value	Effect size**
General Linear Model (GLM)						
Multiple Imputation	1.4 (0.2, 2.5)	0.019	0.30	1.2 (0.1, 2.4)	0.032	0.27
Regression Imputation	1.4 (0.3, 2.5)	0.011	0.31	1.3 (0.2, 2.3)	0.021	0.28
Last Observation Carried Forward	1.3 (0.2, 2.4)	0.018	0.29	1.2 (0.1, 2.3)	0.032	0.27
No imputation for missing data	1.6 (0.5, 2.8)	0.005	0.36	1.5 (0.4, 3.7)	0.010	0.33
Generalised Estimating Equations (GEE)* **						
Multiple Imputation	1.3 (0.2, 2.4)	0.026	0.28	1.2 (-0.0, 2.3)	0.051	0.26
Regression Imputation	1.4 (0.3, 2.4)	0.010	0.30	1.2 (0.2, 2.3)	0.025	0.27
Last Observation Carried Forward	1.3 (0.1, 2.4)	0.028	0.28	1.2 (-0.0, 2.3)	0.057	0.25
No imputation for missing data	1.6 (0.5, 2.6)	0.003	0.34	1.4 (0.4, 2.5)	0.006	0.32

* All results are between group differences ("Offer" compared to "No offer" group), with higher PHQ-9 scores for the "No offer" group.
** Effect size calculation: ES = M1-M2/SD1 (Kazis et al. 1989), using Estimated Marginal Means for M1 and M2, as they take into account baseline PHQ-9 scores, divided by the baseline standard deviation. *** Taking into account practitioner effect (7 practitioners, "Offer group" not treated, and "No offer" group) PHQ-9: Patient Health Questionnaire. AD: Current use of antidepressants. >3LSC: More than 3 long-standing conditions.

5.10.2 Depression assessed at 6 months – secondary analyses (ITT-analyses)

General Linear Model

The between group difference in 6 month depression (PHQ-9) score was 1.2 points in favour of the "Offer" group when controlling for baseline depression (PHQ-9) scores, antidepressant use, the existence of more than three long-standing conditions and gender (95% CI 0.1, 2.4, n=451, p=0.032). When using LOCF for imputation of missing data, results were 1.3 (95% CI 0.2, 2.4, n=458, p=0.018) and 1.2 (95% CI 0.1, 2.3, n=451, p=0.032), and for RI 1.4 (95% CI 0.3, 2.5, n=458, p=0.011) and 1.3 (95% CI 0.2, 2.3, n=451, p=0.021). The between group difference for no imputation of missing values was larger (1.6, 95% CI 0.5, 2.8, n=458, p=0.005) when controlling for PHQ-9 alone, and when also controlling for the other three covariates (1.5, 95% CI 0.4, 3.7, n=451, p=0.010). All results showed lower scores in the "Offer" group.

In summary, between group differences in mean depression (PHQ-9) scores at 6 months ranged from 1.2 to 1.6 with p-values ranging from 0.005 to 0.032, and for the main analysis 1.4 (95% CI 0.2, 2.5, p=0.019), in favour of the "Offer" group.

Generalised Estimating Equations

As the homeopathic intervention was therapist based, the generalised estimating equations (GEE) statistical method was used to account for potential clustering or correlation of patients' outcomes and treatment offered by particular practitioners. GEE analysis was used to compare mean PHQ-9 scores at 6 months post-randomisation between the "Offer" and "No offer" group. As for GLM analyses, two models were applied, one controlling for patients' baseline PHQ-9 scores, and a second also for baseline antidepressant use, the existence of more than 3 long-standing conditions, and gender. Participants in the control group were treated as one cluster in the analysis.

Results of the main GEE analysis, controlling for baseline PHQ-9 scores and using multiple imputation for missing values gave mean depression (PHQ-9) that were 1.3 points (95% CI 0.2, 2.4, n=458) lower in the "Offer" than the "No offer" group (p=0.026) at 6 months. The between group difference was 1.2 (95% CI -0.0, 2.3, n=451, p=0.051) when also controlling for baseline antidepressant use, the existence of more than 3 long-standing conditions and gender. Replacement of missing data using Regression Imputation gave between group differences of 1.4 points (95% CI 0.3, 2.4, n=458, p=0.010) and 1.2 (95% CI 0.2, 2.3, n=451, p=0.027), and for LOCF 1.3 (95% CI 0.1, 2.4, n=458, p=0.028) and 1.2 (95% CI -0.0, 2.3, n=451, p=0.057), in favour of the "Offer" group. For no imputation of missing data results were 1.6 (95% CI 0.5, 2.6, n=458, p=0.003) and 1.4 (95% CI 0.4, 2.5, n=451, p=0.006).

In summary, between group differences in mean depression (PHQ-9) ranged from 1.2 to 1.6 with p-values ≤ 0.05 for six out of eight tests and for two with p-values at 0.051 and 0.057, and for the main GEE analysis 1.3 (95% CI 0.2, 2.4, p=0.026), in favour of the "Offer" group.

Interaction analyses

Interaction analyses, carried out using a General Linear Model with an interaction term for each pre-selected baseline covariate, were carried out to consider the combined effect on the 6 month depression score. The baseline PHQ-9 score, use of antidepressants, number of long-standing conditions (0 to 3 compared to 4 or more LSC), GAD-7 score, depression onset (years/months), employment status, BMI score and alcohol consumption were each tested using the following model:

$$\text{PHQ-9}_{6\text{ months}} = \text{Group}_{BL} + \text{PHQ-9}_{BL} + \text{Interaction}_{BL}\ (\text{Group}_{BL} \times \text{PHQ-9}_{BL})$$

Where: PHQ-$9_{6\ months}$ = PHQ-9 score at 6 months; $Group_{BL}$ = "Offer" group and "No offer" group at baseline; PHQ-9_{BL}= PHQ-9 scores at baseline; $Interaction_{BL}$ = Group at baseline ("Offer group"=1, "No offer" group=0) x PHQ-9 scores at baseline

Results of interaction analyses gave p-values ranging from 0.343 to 0.949 (details not reported), suggesting that there was no evidence that the effect of offer status differed by any of the other variables. Additional tests were run where baseline PHQ-9 values were included all interaction analyses, resulting in p-values from 0.204 to 0.973 (details not reported).

5.10.3 Effect size for the depression outcome (ITT-analyses)

The between group difference in depression (PHQ-9) scores was also quantified by calculating a standardised effect size. This enabled comparison with other trials using different outcome measures (Cohen 1969, 1988). For calculation of the standardised effect size, here reported as Cohen's *d*, the following formula was used (Kazis et al. 1989): ES = M1-M2/SD1. (ES=effect size; M1 = mean PHQ-9 score at baseline; M2 = mean PHQ-9 score at 6 months; SD1=standard deviation for the PHQ-9 score at baseline.) Estimated marginal means were used for calculation of the standardised effect size, as they took into account baseline PHQ-9 values.

The main analysis, using the General Linear Model, controlling for baseline PHQ-9 scores and replacing data using Multiple Imputation, gave an effect size of 0.30 in favour of the "Offer" group. The effect size in the remaining analyses, controlling for baseline PHQ-9,

antidepressant use, the existence of more than 3 long-standing conditions and gender, with imputation for missing data ranged from 0.27 to 0.31, and 0.33 to 0.36 with no imputation for missing data (details in table 20). For analyses using the generalised estimating equations (GEE), which also took into account any clustering or correlation of patients' outcomes and treatment offered by particular practitioners, effect sizes ranged from 0.25 to 0.30 with imputation for missing data in favour of the "Offer" group, and 0.32 and 0.34 with no imputation for missing data.

According to so-called "rules of thumb" presented by Cohen (1969, 1988) and Lipsey (1990) the effect size is small if d = 0.2 (Cohen 1969, 1988) or ≤ 0.32 (Lipsey 1990); medium if d = 0.5 or 0.33-0.55; and large if d = 0.8 or 0.56-1.2. This suggests there was a "small" effect size of the offer of treatment provided by a homeopath. Cohen himself warned that such "rules of thumb" should be used with caution. Further interpretation of the results suggests that Cohen's d of 0.3 indicates that 62 % of the "Offer" group's PHQ-9 score was below (better than) than the mean for the "No offer" group score and 88 % of the "Offer" and "No offer" group patients' results overlapped (Magnusson 2014). The number needed to be offered treatment by a homeopath (NNO) in order for one patient to improve was 11. Moreover, if a random selection of trial patients were to be made, there would be a 58 % chance that an "Offer" group patient would have better (lower) depression scores than a "No offer" group patient.

In summary, the intention-to-treat analysis showed a small effect size (d=0.30, range 0.25–0.36) of the offer of treatment provided by homeopaths with about 11 patients needed to be offered treatment by a homeopath (NNO) in order for one patient to improve.

5.11 Anxiety at 6 months: Intention-to-treat analyses

The influence of baseline covariates on GAD-7 scores at 6 months

A hierarchical model similar to the one used for assessing the influence of baseline covariates on depression (PHQ-9) scores at 6 months was applied for anxiety (GAD-7) scores at 6 months. The only difference in the procedure was that the baseline anxiety (GAD-7) score was listed first and PHQ-9 was fourth in the model:

1) Anxiety (GAD-7) scores
2) Current antidepressant use
3) More than 3 long-standing conditions
4) Depression (PHQ-9) score
5) The first onset of depression
6) Employment status
7) BMI score
8) Alcohol units per week
9) Deprivation (IMD) quintile
10) Gender
11) Age

After running all tests, the following six covariates remained in the model (unstandardised coefficients with standard deviation and p-values reported):

1) Anxiety (GAD-7) score: 0.472 (SD 0.066), p=0.000
2) Current antidepressant use (yes): 0.702 (SD 0.501), p=0.162
3) More than 3 long-standing conditions (yes): 1.152 (SD 0.530), p=0.030
4) Depression (PHQ-9) score: 0.159 (SD 0.069), p=0.022
5) Employment status BL: -1.067 (SD 0.563), p=0.059
6) Age BL: -0.060 (SD 0.020), p=0.003

The model explained 28.7 % of the variance (R^2=0.287). The most significant contributor to the model was the baseline GAD-7 score, which on its own contributed to 22.4 % of the variance (R^2=0.224).

A histogram showed that the dependent variable (GAD-7 at 6 months) had a normal distribution. A scatterplot showed homoscedasticity (residuals were spread out) and there seemed to be linearity of the model. A P-P Plot test of the regression standardised residual showed that the observed data was fairly similar to the expected data (they fell on the straight line). Results may be seen in figures 6, 7 and 8 (Histogram, Normal P-Plot of Regression Standardized Residual and Scatterplot for Regression Standardized Residual/Regression Standardized Predicted Value).

In conclusion, it seemed reasonable to apply the model including baseline GAD-7 scores, antidepressant use, the existence of more than 3 long-standing conditions, PHQ-9 scores, employment status, and age as covariates to assess 6 month outcomes by the use of a marginal general linear model and general estimating equations, and for regression imputation.

5.11.1 Anxiety assessed at 6 months – primary analysis (ITT-analysis)

The main method of assessing anxiety (GAD-7) scores, the General Linear Model with baseline GAD-7 scores as covariate and Multiple Imputation for replacing missing data, gave a between group difference in favour of the "Offer" group of 1.5 (95% CI 0.5, 2.5, n=456, p=0.003) (table 21: Anxiety outcomes at 6 months – Intention-to-treat analysis).

Table 21. Anxiety outcomes at 6 months – Intention to treat analysis

Baseline covariates controlled for	**GAD-7 (n=456)**			**GAD-7, AD, >3LSC, PHQ-9, Employment, Age (n=426)**		
	Mean (95% CI)*	**p-value**	**Effect size****	**Mean (95% CI)**	**p-value**	**Effect size****
General Linear Model (GLM)						
Multiple Imputation (456/426)	1.5 (0.5, 2.5)	0.003	0.33	1.2 (0.2, 2.2)	0.019	0.26
Regression Imputation (456/426)	1.4 (0.4, 2.4)	0.005	0.30	1.2 (0.2, 2.2)	0.015	0.26
Last Observation Carried Forward	1.4 (0.5, 2.4)	0.004	0.31	1.1 (0.1, 2.1)	0.027	0.24
No imputation for missing data	1.2 (0.2, 2.3)	0.023	0.26	1.0 (-0.0, 2.1)	0.060	0.21
Generalised Estimating Equations (GEE)***						
Multiple Imputation (456/426)	1.5 (0.1, 2.9)	0.042	0.32	1.2 (-0.2, 2.5)	0.092	0.25
Regression Imputation (456/426)	1.3 (0.2, 2.5)	0.022	0.29	1.2 (0.0, 2.3)	0.045	0.25
Last Observation Carried Forward	1.4 (0.1, 2.7)	0.035	0.30	1.1 (-0.2, 2.3)	0.090	0.23
No imputation for missing data	1.2 (-0.3, 2.6)	0.108	0.25	1.0 (-0.4, 2.4)	0.172	0.20

* All results are between group differences ("Offer" compared to "No offer" group), with higher PHQ-9 scores for the "No offer" group.
** Effect size calculation: ES = M1-M2/SD1 (Kazis et al. 1989), using Estimated Marginal Means for M1 and M2, as they take into account baseline GAD-7 scores, divided by the baseline standard deviation.
*** Taking into account practitioner effect (7 practitioners, "Offer group" not treated, and "No offer" group)
PHQ-9: Patient Health Questionnaire. AD: Current use of antidepressants. >3LSC: More than 3 long-standing conditions.

5.11.2 Anxiety assessed at 6 months – secondary analyses (ITT-analyses)

General Linear Model

The remaining analyses, using either baseline GAD-7 alone as covariate or the full model described in the previous section, and using either Regression Imputation or LOCF for imputation of missing data resulted in between group differences ranged from 1.1 to 1.4, with p-values ranging from 0.004 to 0.027, all in favour of the "Offer" group. Results for non-imputed data were 1.2 and 1.0 with p-values at 0.023 and 0.060. Details can be found in table 21.

In summary, between group differences in mean anxiety (GAD-7) scores ranged from 1.1 to 1.4 with p-values ranging from 0.004 to 0.027 for data with imputation for missing values, and for the main analysis 1.5 (95% CI 0.5, 2.5, p=0.003), in favour of the "Offer" group. Analyses using non-imputed data gave between group differences on GAD-7 at 1.2 and 1.0 points (p=0.023 and 0.060).

Generalised Estimating Equations

Results of the analyses also taking into account practitioner effects when assessing anxiety (GAD-7) scores ranged from 1.0 to 1.5, in favour of the "Offer" group, with statistically significant results for analyses taking into account patients baselined anxiety scores and using MI, RI or LOCF for imputation of missing data (p-values 0.042, 0.022 and 0.035), and for the analysis taking into account all included baseline covariates and using RI for missing data (p=0.045). For the remaining two analyses using MI and LOCF for missing data, results were not statistically significant (p=0.090, 0.092). Analyses with no imputation for missing data were less positive, with between group differences of 1.0 and 1.2 points, and p-values at 0.108 and 0.172.

In summary, between group differences in mean anxiety (GAD-7) scores ranged from 1.0 to 1.5 with p-values ≤ 0.05 for four out of eight tests, in favour of the "Offer" group. Results were more positive for assessments using imputation for missing data, than no imputation for missing data.

5.11.3 Effect size for the anxiety outcome (ITT-analyses)

The main analysis (GLM with MI for missing data) gave a standardised effect size of Cohen's *d* = 0.33. Remaining GLM and GEE analyses gave effect sizes ranging from *d* = 0.20 to 0.32, with the poorest results for data with no imputation for missing data (details in table 21).

5.12 Summary of the intention-to-treat analyses

Depression outcomes at 6 months

The main intention-to-treat analysis of patients' self-reported depression (PHQ-9) scores at 6 months post-randomisation showed a mean between group difference of 1.4 points (95% CI 0.2, 2.5, n=458) in favour of the "Offer" group (p=0.019) when using a general linear model (GLM) controlling for baseline PHQ-9 scores and using multiple imputation (MI) for missing data.

Similar results were found for secondary analyses (table 20: Depression outcomes at 6 months – Intention-to-treat analysis) including GLM-analyses and analyses using generalised estimating equations (GEE), all either controlling for baseline PHQ-9 scores or including all baseline covariates influencing 6 month results (at p=0.2 level), and using either Multiple Imputation (MI), Regression Imputation (RI), last observation carried forward (LOCF) for replacing missing data, or with no replacement of missing data. For GLM-analyses mean between group differences ranged from 1.2 to 1.6 points on PHQ-9 in favour of the "Offer" group (p=0.005–0.032), but with 95 % Confidence Intervals from 0.4 to 3.7 at its worst (widest 95% CI), and 0.3 to 2.5 at its best (narrowest 95% CI). For GEE-analyses, mean between group differences ranged from 1.2 to 1.6 points, with 95% CI from -0.0 to 2.3 at its worst (widest 95% CI), and 0.5 to 2.6 at the best (narrowest 95% CI). Two out of 16 tests gave p-values at 0.051 and 0.057, whereas the remaining 14 tests gave p-values in the range from 0.003 to 0.032.

For the primary analysis, we can be 95 % confident that the effect of the offer of treatment by a homeopath on the mean PHQ-9 score at 6 months post randomisation in the

population lies somewhere between 0.2 and 2.5 points, in favour of the "Offer" group, with the mean of 1.4 points being the "best guess". This result gave a small standardized effect size (Cohen's *d*=0.30) of the offer of treatment provided by a homeopath for patients with self-reported depression. Similar effect sizes were found for secondary analyses (range of Cohen's *d*=0.25–0.36) This effect size suggests that the "best guess" would be that about 11 patients need to be offered (NNO) treatment by a homeopath in order for one patient to have improved depression (PHQ-9) scores. The identified 95 % Confidence Intervals suggested that the result in the population would be in the range from no effect of the offer of treatment to an effect that would be up to 140 % larger than the effect size identified using the mean difference. Due to large confidence intervals, no firm conclusion can be drawn as to the effect of the offer of treatment, although the "best guess" would suggest a small standardized effect size.

Anxiety outcomes at 6 months

The main intention-to-treat analysis of patients' self-reported anxiety (GAD-7) scores at 6 months post-randomisation showed a mean between group difference of 1.5 points (95% CI 0.5, 2.5, n=456) in favour of the "Offer" group (p=0.003) when using a general linear model (GLM) controlling for baseline GAD-7 scores and using multiple imputation (MI) for missing data.

Results for secondary analyses on anxiety outcomes (table 21: Anxiety outcomes at 6 months – Intention-to-treat analysis) were calculated using the same approach as for depression outcomes, including methods for imputing missing data, but by using baseline GAD-7 (instead of PHQ-9) scores. For GLM-analyses mean between group differences ranged from 1.0 to 1.4 points on GAD-7 in favour of the "Offer" group (p=0.004–0.060), with 95 % Confidence Intervals from -0.0 to 2.1 at its worst (widest 95% CI), and 0.2 to 2.2 at its best (narrowest 95% CI). For GEE-analyses, mean between group differences ranged from 1.0 to 1.5 points, with 95 % CI from -0.3 to 2.6 at its worst (widest 95% CI), and 0.0 to 2.3 at the best (narrowest 95% CI). Five out of 16 tests gave p-values $\geq$ 0.05 (0.060, 0.090, 0,092, 0.108 and 0.172), with the poorest results for data with no imputation for missing values. The remaining 11 tests gave p-values in the range from 0.003 to 0.032.

For the primary analysis, we can be 95 % confident that the effect of the offer of treatment by a homeopath on the mean GAD-7 score at 6 months post randomisation in the population lies somewhere between 0.5 and 2.5 points, in favour of the "Offer" group, with the mean of 1.5 points being the "best guess". This result gave a small standardized effect size (Cohen's *d*=0.33) for anxiety of the offer of treatment provided by a homeopath for patients with self-reported depression. Effect sizes were slightly smaller for most secondary analyses (range of Cohen's *d*=0.20–0.32) This effect size suggests that the "best guess" would be that from 11 to 17 need to be offered (NNO) treatment by a homeopath in order for one patient to have improved anxiety (GAD-7) scores. The identified 95 % Confidence Intervals suggested that the result in the population would be in the range from a slight negative effect to an effect that would be up to 140 % larger than the effect size identified using the mean difference. Due to large confidence intervals, also below zero, no firm conclusion can be drawn as to the effect of the offer of treatment, although the "best guess" would suggest a small standardized effect size.

5.13 Depression at 6 months: Instrumental variables analyses

The ITT analysis included patients in the "Offer" group who received treatment and also those who did not. If there is an effect of the intervention, then the ITT analysis "watered it down" (Becque & White 2008) due to the fact that six out of ten patients did not receive the treatment offered. In order to assess the effectiveness of treatment received, the protocol stated that a complier average causal effect (CACE) analysis was to be carried out. An Instrumental Variables (IV) analysis was carried out, as this is a form of CACE analysis which controls for baseline covariates. IV-analyses compared outcomes for patients in the "Offer" group who received treatment by a homeopath, compared to those in the "No offer" group who would have received treatment by a homeopath had they been offered it.

Assumptions for carrying out CACE/IV-analyses

As pointed out in section 4.1.14 (The effectiveness of treatment provided by homeopaths for depressed patients), CACE-analysis (or IV-analysis) is carried out under two assumptions (Hewitt et al. 2006). The first assumption is that the probability of non-compliance with treatment, or the offer of treatment, is equal in the two groups. For this

trial this meant that the proportion of patients in the "No offer" group, who would not have received treatment if they had been offered it, was assumed to be similar to the proportion of patients in the "Offer" group who did not receive treatment.

The second assumption is that offer patients treatment does not in itself have an effect. This means that patients who have received an offer of treatment provided by a homeopath, but who decides not to take up the offer, should not do better than patients in who have not received the offer ("No offer" group). Further assessment of this assumption is considered in section 5.16.1 (Comparison of ITT-, IV- and PP-analyses).

Given these two assumptions, the proportion of patients who would not have been treated in the "No offer" group, would have been similar to the proportion of patients who were not treated in the "Offer" group, and their outcomes would be comparable. The outcomes for patients in the "No offer" group who would have been treated had they received the offer, could therefore be calculated and their results could be compared to patients in the "Offer" group who received treatment.

Potential effect of being an accepter

Another question was whether being an accepter affects results. An accepter is here understood as someone who accepted the offer of treatment and who received treatment. (Some patients accepted the offer, but did not come for treatment.) Are accepters and non-accepters different in ways that will influence the outcomes? If there is no effect of being an accepter, then the results of IV and per-protocol analyses would be similar. In order to consider this, a per-protocol analysis, comparing those in the "Offer" group who received treatment provided by a homeopath with all patients in the "No offer" group, will also be presented.

Comparability of baseline covariates for accepters and non-accepters

Moreover baseline differences between accepters and non-accepters were also compared (table 22: Baseline demographics – Offer group treated & not treated; table 23: Baseline health measures – Offer group treated & not treated; and table 24: Baseline medication – Offer group treated & not treated). No statistically significant differences were found for

the two health outcomes (PHQ-9 and GAD-7). The only between group difference in baseline covariates that reached statistical significance was employment status, where accepters were more likely to be employed than non-accepters (52.9% versus 29.5%, p=0.025), but no significant differences were found for deprivation quintiles. There was a trend towards a statistically significant difference in BMI categories (p=0.057), where the main difference was a higher proportion of accepters than non-accepters with a healthy weight, but fewer non-accepters responded to this question (82% versus 93%), and there was no significant difference for the average BMI score (p=0.663). It seemed reasonable to assume that baseline covariates would not significantly influence any potential between group differences identified through IV-analyses.

Table 22. Baseline demographics – Offer group treated & not treated

		Not treated			Treated			
Variable		**n**	**Mean / %**	**SD**	**n**	**Mean / %**	**SD**	**p-value**
Gender	Female	43	38.7 %		**28**	**37.8 %**		
	Male	68	61.3%		**46**	**62.2%**		**1.000**
Age			56.8	(16.5)		**54.3**	**(12.4)**	**0.241**
Age category	18 – 19	2	1.8 %		**0**	**1.1 %**		
	20 – 29	7	6.3 %		**3**	**5.4 %**		
	30 – 39	10	9.0 %		**5**	**8.1 %**		
	40 – 49	13	11.7 %		**17**	**16.2 %**		
	50 – 59	26	23.4 %		**30**	**30.3 %**		
	60 – 69	29	26.1 %		**10**	**21.1 %**		
	70 – 79	19	17.1 %		**8**	**14.6 %**		
	80 – 85	5	4.5 %		**1**	**3.2 %**		**0.280**
Children ≤ 2 years	Yes	7	6.3 %		**2**	**2.7 %**		**0.315**
Pregnant	Yes	0	0.0 %		**0**	**0.0 %**		**1.000**
Ethnic group	British	108	97.3 %		**71**	**95.9 %**		
	Non-British	3	2.7 %		**3**	**4.1 %**		**0.685**
City/Borough	Barnsley	8	7.2 %		**10**	**13.7 %**		
	Doncaster	32	28.8 %		**15**	**20.5 %**		
	Rotherham	19	17.1 %		**14**	**19.2 %**		
	Sheffield	52	46.8 %		**34**	**46.6 %**		**0.364**
Employed	Yes	31	29.5 %		**33**	**52.9 %**		
	No	74	70.5 %		**37**	**47.1 %**		**0.025**
IMD quintile	1 (least deprived)	5	4.5 %		**6**	**8.1 %**		
	2	18	16.2 %		**16**	**21.6 %**		
	3	14	12.6 %		**12**	**16.2 %**		
	4	23	20.7 %		**11**	**14.9 %**		
	5 (most deprived)	51	45.9 %		**29**	**39.2 %**		**0.496**

Categorical variables tested using chi-square test (Fisher's Exact Test / Pearson Chi-Square Test)
Continuous variables tested using an Independent Sample's T-Test

Table 23. Baseline health measures – Offer group accepters & non-accepters

		Not treated			Treated			
Variable		**n**	**Mean / %**	**SD**	**n**	**Mean / %**	**SD**	**p-value**
PHQ-9 score			17.3	(4.5)		**16.4**	**(4.5)**	**0.187**
PHQ-9 category	Moderate (10 – 14)	33	29.7 %		**31**	**41.9 %**		
	Moderately severe (15 – 19)	43	38.7 %		**26**	**35.1%**		
	Severe (20 – 27)	35	31.5 %		**17**	**23.0%**		**0.201**
Depression onset	Acute (< 3 months)	2	3.2%		**0**	**0.0 %**		
	Subacute (3 months - < 1 year)	3	4.8%		**2**	**3.6 %**		
	Chronic (short) (1 - < 2 years)	5	8.1%		**7**	**12.5 %**		
	Chronic (long) (2 - < 5 years)	8	12.9%		**2**	**3.6 %**		
	Chronic (very long) (5 years +)	44	71.0%		**45**	**80.4 %**		**0.210**
Depression episode onset	Acute (< 3 months)	4	10.3 %		**6**	**15.4 %**		
	Subacute (3 months - < 1 year)	3	7.7 %		**5**	**12.8 %**		
	Chronic (short) (1 - < 2 years)	5	12.8 %		**4**	**10.3 %**		
	Chronic (long) (2 - < 5 years)	3	7.7 %		**5**	**12.8 %**		
	Chronic (very long) (5 years +)	4	10.3 %		**5**	**12.8 %**		
	Chronic (length unspecified)	18	46.2 %		**12**	**30.8 %**		
	Periodic	1	2.6 %		**2**	**5.1 %**		
	None	1	2.6 %		**0**	**0.0%**		**0.762**
GAD-7 score			13.5	(4.4)		**13.3**	**(5.3)**	**0.787**
GAD-7 category	Normal (0 – 4)	3	2.7 %		**3**	**4.1 %**		
	Mild (5 – 9)	17	15.3 %		**15**	**20.5 %**		
	Moderate (10 – 14)	44	39.6 %		**24**	**32.9 %**		
	Severe (15 – 21)	47	42.3 %		**31**	**42.5 %**		**0.681**

Table 23. Baseline health measures – Offer group accepters & non-accepters (continued)

BMI score			28.51	(7.05)		**28.05**	**(5.89)**	**0.663**
BMI category	Underweight (< 18.5)	3	2.7 %		**0**	**0.0 %**		
	Healthy weight (18.5 – 24.9)	28	25.2 %		**30**	**40.5 %**		
	Overweight (25.0 – 29.9)	25	22.5 %		**12**	**16.2 %**		
	Obese (30.0 – 39.9)	29	26.1 %		**22**	**29.7 %**		
	Morbidly obese (40.0 +)	6	5.4 %		**5**	**6.8 %**		
	Not reported	20	18.0 %		**5**	**6.8 %**		**0.057**
LSC	Yes	98	90.7 %		**67**	**90.5 %**		
	No	10	9.3 %		**7**	**9.5 %**		**1.000**
LSC (n)			3.04	(1.87)		**2.96**	**(1.63)**	**0.772**
LSC	0-3 conditions	67	62.0 %		**50**	**67.6 %**		
	> 3 conditions	41	38.0 %		**24**	**32.4 %**		**0.529**
Alcohol consumption	Days last week		1.54	(2.14)		**1.82**	**(3.94)**	**0.552**
	Units last week		6.29	(15.75)		**7.97**	**(18.63)**	**0.508**

LSC: Long-standing conditions
Categorical variables tested using chi-square test (Fisher's Exact Test / Pearson Chi-Square Test)
Continuous variables tested using an Independent Sample's T-Test

Table 24. Baseline medication – Offer group accepters & non-accepters

		Not treated			Treated			
Variable		**n**	**Mean / %**	**SD**	**n**	**Mean / %**	**SD**	**p-value**
Antidepressant use (current)	Yes	50	45.0 %		**31**	**41.9 %**		
	No							
	Unknown	61	55.0 %		**43**	**58.1 %**		**0.763**
Antidepressant use (past)	Yes	56	61.5 %		**47**	**72.3 %**		
	No	35	38.5 %		**18**	**27.7 %**		**0.174**
	Unknown							
Medication (all types)			4.94	(4.14)		**4.24**	**(3.65)**	**0.246**

Categorical variables tested using chi-square test (Fisher's Exact Test / Pearson Chi-Square Test)
Continuous variables tested using an Independent Sample's T-Test

5.13.1 Effectiveness of treatment received from homeopaths for depression (IV-analyses)

IV-analyses were carried out assessing between group differences in changes in depression (PHQ-9) scores at 6 months, comparing results for patients in the "Offer" group who received treatment provided by a homeopath with patients in the "No offer" group who would have received treatment had they been offered it. As for ITT-analyses, tests assessing 6 month depression (PHQ-9) scores controlled for baseline PHQ-9 scores, as well as the other baseline covariates that were used for ITT-analyses, and missing data was replaced using MI, RI and LOCF, with MI used for the main analysis.

In the primary IV-analysis "Offer" group patients who received treatment by a homeopath had on average 2.6 points (95% CI 0.5, 4.7, n=458, p=0.018) lower depression (PHQ-9) scores at 6 months post-randomisation compared to "No offer" group patients who would have received treatment had they been offered it, when controlling for baseline PHQ-9 scores and using MI for missing values. Results are presented in table 25 (Depression outcomes at 6 months – Instrumental Variables analysis).

Table 25. Depression outcomes at 6 months – Instrumental Variables analysis

Baseline covariates controlled for	**PHQ-9 (n=458)**			**PHQ-9, AD, >3LSC, gender (n=451)**		
	Mean (95% CI)*	**p-value**	**Effect size****	**Mean (95% CI)**	**p-value**	**Effect size****
Multiple Imputation	2.6 (0.5, 4.7)	0.018	0.57	2.3 (0.2, 4.5)	0.031	0.52
Regression Imputation	2.8 (0.7, 4.9)	0.008	0.61	2.5 (0.5, 4.6)	0.015	0.55
Last Observation Carried Forward	2.6 (0.5, 4.7)	0.017	0.56	2.3 (0.2, 4.4)	0.031	0.50
No imputation for missing data	2.9 (0.7, 5.0)	0.010	0.63	2.6 (0.5, 4.8)	0.018	0.57

* All results are differences between patients who received treatment by homeopaths and those in the "No offer" group who would have received treatment had they been offered it.

** Effect size calculation: ES = M1-M2/SD1 (Kazis et al. 1989), using between group differences calculated using IV-analysis, divided by baseline standard deviation.

PHQ-9: Patient Health Questionnaire. AD: Current use of antidepressants. >3LSC: More than 3 long-standing conditions.

The between group difference in 6 month depression (PHQ-9) score was 2.3 points (95% CI 0.2, 4.5, n=451, p=0.031) in favour of patients who received treatment by a homeopath when using MI for missing values and controlling for baseline depression (PHQ-9) scores, antidepressant use, the existence of more than three long-standing conditions and gender.

When using LOCF for imputation of missing data, results were 2.6 (95% CI 0.5, 4.7, n=458, p=0.017) and 2.3 (95% CI 0.2, 4.4, n=451, p=0.031), and for RI 2.8 (95% CI 0.7, 4.9, n=458, p=0.008) and 2.5 (95% CI 0.5, 4.6, n=451, p=0.015). The between group difference for no imputation of missing values was slightly larger (2.9, 95% CI 0.7, 5.0, n=458, p=0.010) when controlling for PHQ-9 alone, and when also controlling for the other three covariates (2.6, 95% CI 0.5, 4.8, n=451, p=0.018) compared to results with imputation for missing data. All results were in favour of patients who received treatment by a homeopath.

In summary, between group differences in mean depression (PHQ-9) scores at 6 months ranged from 2.3 to 2.9 with p-values ranging from 0.008 to 0.031, and for the main analysis 2.6 (95% CI 0.5, 4.7, p=0.018), in favour of "Offer" group patients who received treatment by a homeopath, compared to those in the "No offer" group who would have received treatment by a homeopath had they been offered it.

5.13.2 Effect size for the depression outcome (IV-analysis)

Using Cohen's (1969, 1988) and Lipsey's (1990) "rules of thumb" the standardised effect size of d = 0.57, could be categorised as at least medium (0.5 or 0.33 – 0.55). This would mean that for 72 % of patients who received treatment by a homeopath the PHQ-9 score was below (better than) than the mean for those in the "No offer" group who would have received treatment by a homeopath had they been offered it. About 78 % of the "Offer" group patients who received treatment by a homeopath and the "No offer" group patients' who would have received treatment had they been offered it overlapped (Magnusson 2014). The number needed to be offered treatment by a homeopath (NNT) in order for one patient to improve was 6. Moreover, if a random selection of trial patients were to be made, there would be a 66 % chance that a patient in the "Offer" group who received treatment would have better (lower) depression scores than a "No offer" group patient who would have received treatment had it been offered. Remaining IV-analyses gave effect sizes ranging from d = 0.50 to 0.61 for data with imputation for missing data, and 0.57 and 0.63 without imputation for missing data (details in table 25).

5.14 Anxiety at 6 months: An instrumental variables analysis

5.14.1 Effectiveness of treatment received from homeopaths (IV-analyses)

In the primary IV-analysis “Offer” group patients who received treatment by a homeopath had on average 2.8 points (95% CI 0.9, 4.8, n=455, p=0.004) lower anxiety (GAD-7) scores at 6 months post-randomisation compared to “No offer” group patients who would have received treatment had they been offered it, when controlling for baseline GAD-7 scores and using MI for missing values. Results are presented in table 26 (Anxiety outcomes at 6 months – Instrumental Variables analysis).

The between group difference in 6 month depression (GAD-7) score was 2.4 points (95% CI 0.4, 4.3, n=426, p=0.018) in favour of patients who received treatment by a homeopath when using MI for missing values and controlling for all included baseline covariates. When using LOCF for imputation of missing data, results were 2.7 (95% CI 0.8, 4.6, n=455, p=0.006) and 2.2 (95% CI 0.3, 4.1, n=426, p=0.026), and for RI 2.8 (95% CI 0.7, 4.8, n=455, p=0.008) and 2.3 (95% CI 0.3, 4.4, n=426, p=0.027). The between group difference for no imputation of missing values was slightly smaller (2.3, 95% CI 0.3, 4.3, n=455, p=0.048) when controlling for GAD-7 alone, and when also controlling for the other covariates (2.0, 95% CI -0.1, 4.0, n=426, p=0.058) compared to results with imputation for missing data. All results were in favour of patients who received treatment from a homeopath.

In summary, between group differences in mean anxiety (GAD-7) scores at 6 months ranged from 2.0 to 2.8 with p-values ranging from 0.004 to 0.058, and for the main analysis 2.8 (95% CI 0.9, 4.8, p=0.004), in favour of "Offer" group patients who received treatment by a homeopath, compared to those in the “No offer” group who would have received treatment by a homeopath had they been offered it.

Table 26. Anxiety outcomes at 6 months – Instrumental Variables analysis

Baseline covariates controlled for	GAD-7 (n=455)			GAD-7, AD, >3LSC, PHQ-9, Employment, Age (n=426)		
	Mean (95% CI)*	p-value	Effect size**	Mean (95% CI)	p-value	Effect size**
Multiple Imputation	2.8 (0.9, 4.8)	0.004	0.61	2.4 (0.4, 4.4)	0.018	0.51
Regression Imputation	2.8 (0.7, 4.8)	0.008	0.58	2.3 (0.3, 4.4)	0.027	0.51
Last Observation Carried Forward	2.7 (0.8, 4.6)	0.006	0.58	2.2 (0.3, 4.1)	0.026	0.48
No imputation for missing data	2.3 (0.3, 4.3)	0.027	0.48	2.0 (-0.1, 4.0)	0.058	0.42

* All results are differences between patients who received treatment by homeopaths and those in the "No offer" group who would have received treatment had they been offered it.

** Effect size calculation: ES = M1-M2/SD1 (Kazis et al. 1989), using between group differences calculated using IV-analysis, divided by the baseline standard deviation.

GAD-7: Generalized Anxiety Disorder Questionnaire. PHQ-9: Patient Health Questionnaire. AD: Current use of antidepressants. >3LSC: More than 3 long-standing conditions.

5.14.2 Effect size for the anxiety outcome (IV-analysis)

The main analysis, controlling for baseline GAD-7 scores and using MI for missing data, gave a standardised effect size of Cohen's d = 0.61. Remaining IV-analyses gave effect sizes ranging from d = 0.42 to 0.58, with the poorest results for data with no imputation for missing data (details in table 26).

5.15 Summary of the instrumental variables analyses

Depression outcomes at 6 months

The main instrumental variables (IV) analysis of patients' self-reported depression (PHQ-9) scores at 6 months post-randomisation showed a mean between group difference of 2.6 points (95% CI 0.5, 4.7, n=458) in favour of treated patients in the "Offer" group (p=0.018) when controlling for baseline PHQ-9 scores and using multiple imputation (MI) for missing data.

Similar results were found for secondary analyses (table 25: Depression outcomes at 6 months – Instrumental Variables analysis), either controlling for baseline PHQ-9 scores or including all baseline covariates influencing 6 month results (at p=0.2 level), and using either Multiple Imputation (MI), Regression Imputation (RI), last observation carried

forward (LOCF) for replacing missing data, or with no replacement of missing data. Mean between group differences ranged from 2.3 to 2.8 points on PHQ-9 in favour of patients who received treatment by a homeopath (p=0.010–0.031), with 95 % Confidence Intervals from 0.7 to 5.0 at its worst (widest 95% CI), and 0.5 to 4.6 at its best (narrowest 95% CI).

For the primary analysis, we can be 95 % confident that the effect of treatment received by a homeopath on the mean PHQ-9 score at 6 months post randomisation in the population lies somewhere between 0.5 and 4.7 points, in favour of patients in the "Offer" group who received treatment by a homeopath, with the mean of 2.6 points being the "best guess". This result gave a medium effect size (Cohen's *d*=0.57) for self-reported depression for patients in the "Offer" group treated by homeopaths. Similar effect sizes were found for secondary analyses (range of Cohen's *d*=0.50–0.63). This effect size suggests that the "best guess" would be that about 6 patients need to be treated (NNT) by a homeopath in order for one patient to have improved depression (PHQ-9) scores. The identified 95 % Confidence Intervals suggested that the result in the population would be in the range from less than a small effect to a large effect (90% higher than the effect size identified using the mean). Due to large confidence intervals, no firm conclusion can be drawn as to the effect of treatment provided by homeopaths, although it would seem reasonable to assume that it would lie in the range from a small to a large effect size, and the "best guess" would suggest a medium standardized effect size.

Anxiety outcomes at 6 months

The main instrumental variables (IV) analysis of patients' self-reported anxiety (GAD-7) scores at 6 months post-randomisation showed a mean between group difference of 2.8 points (95% CI 0.9, 4.8, n=455) in favour of treated patients in the "Offer" group (p=0.004) when controlling for baseline GAD-7 scores and using multiple imputation (MI) for missing data.

Similar results were found for secondary analyses (table 26: Anxiety outcomes at 6 months – Instrumental Variables analysis), either controlling for baseline GAD-7 scores or including all baseline covariates influencing 6 month results (at p=0.2 level), and using either Multiple Imputation (MI), Regression Imputation (RI), last observation carried forward (LOCF) for replacing missing data, or with no replacement of missing data. Mean

between group differences ranged from 2.0 to 2.8 points on GAD-9 in favour of the treated patients in the "Offer" group (p=0.006–0.058), with 95 % Confidence Intervals from 0.3 to 4.4 at its worst (widest 95% CI), and 0.8 to 4.6 at its best (narrowest 95% CI). One out of eight statistical tests resulted in a p-value ≥ 0.05 (p=0.058), with the lower end of the 95 % Confidence Interval just below zero (-0.1). The remaining seven tests gave p-values in the range from 0.004 to 0.027.

For the primary analysis, we can be 95 % confident that the effect of treatment received by a homeopath on the mean GAD-7 score at 6 months post randomisation in the population lies somewhere between 0.9 and 4.8 points, in favour of patients in the "Offer" group who received treatment by a homeopath, with the mean of 2.8 points being the "best guess". This result gave at least a medium effect size (Cohen's *d*=0.61) for self-reported anxiety for patients in the "Offer" group treated by homeopaths. Slightly smaller, medium effect sizes were found for secondary analyses (range of Cohen's *d*=0.48–0.58). This size suggests that the "best guess" would be that about 5 patients need to be treated (NNT) by a homeopath in order for one patient to have improved anxiety (GAD-7) scores. The identified 95 % Confidence Intervals suggested that the result in the population would be in the range from a small effect to a large effect (67% higher than the effect size identified using the mean). Due to large confidence intervals, no firm conclusion can be drawn as to the effect of treatment provided by homeopaths, although it would seem probable that it would lie in the range from a small to a large effect size, and the "best guess" would suggest a medium standardized effect size.

5.16 Per-protocol analyses

Per-protocol (PP) analyses were not included in the protocol for the trial, but were carried out to provide additional information and in particular to consider the potential effect of receiving the offer of treatment. IV-analyses were carried out under the assumption that there was no effect of the offer of treatment. In order for this to be true, the results of IV-analyses should in principle give values in between ITT- and PP-analyses (Greenland 2000).

Depression outcomes (PHQ-9), assessed using the general linear model (GLM), showed between group differences in favour of treated patients in the "Offer" group, compared to "No offer" group patients, with mean values ranging from 2.3 (95% CI 0.9, 3.8, n=398, p=0.002) when using last observation carried forward (LOCF) for missing data, to 2.3 (95% CI 0.9, 3.8, n=398, p=0.002) when using multiple imputation for missing data, when controlling for baseline PHQ-9 scores. When controlling for all baseline covariates included in the model tested in the ITT- and IV-analyses, results ranged from 2.1 (95% CI 0.7, 3.5, n=393, p=0.003) to 2.2 (95% CI 0.8, 3.7, n=393, p=0.003). Between group differences were slightly larger when using no imputation for missing data (table 27: Depression outcomes at 6 months – Per protocol analysis). All results were in favour of treated patients.

Anxiety outcomes (GAD-9) showed between group differences in favour of treated patients in the "Offer" group, compared to "No offer" group patients, with mean values ranging from 2.34 (95% CI 1.05, 3.63, n=396, p<0.000) when using regression imputation (RI) for missing data, to 2.73 (95% CI 1.40, 4.05, n=396, p<0.000) when using multiple imputation for missing data, when controlling for baseline GAD-7 scores. When controlling for all baseline covariates included in the model tested in the ITT- and IV-analyses, results ranged from 2.1 (95% CI 0.8, 3.4, n=369, p=0.001) to 2.3 (95% CI 1.0, 3.7, n=369, p=0.001). Between group differences were slightly smaller when using no imputation for missing data (table 28: Anxiety outcomes at 6 months – Per protocol analysis).

Effect sizes (Cohen's *d*) ranged from 0.47 to 0.54 for the depression outcome, and 0.45 to 0.59 for the anxiety outcome, when using imputation methods for missing data. Effect sizes were slightly higher for depression and lower for anxiety when using no imputation for missing data (tables 27 and 28).

Table 27. Depression outcomes at 6 months – Per protocol analysis

Baseline covariates controlled for	PHQ-9 (n=398)			PHQ-9, AD, >3LSC, gender (n=393)		
	Mean (95% CI)*	p-value	Effect size**	Mean (95% CI)	p-value	Effect size**
Multiple Imputation	2.3 (0.9, 3.8)	0.002	0.51	2.2 (0.8, 3.7)	0.003	0.49
Regression Imputation	2.2 (0.8, 3.7)	0.002	0.49	2.1 (0.7, 3.5)	0.003	0.47
Last Observation Carried Forward	2.3 (0.9, 3.8)	0.002	0.51	2.2 (0.8, 3.7)	0.003	0.49
No imputation for missing data	2.5 (1.0, 3.9)	0.001	0.54	2.6 (0.9, 3.8)	0.002	0.52

* All results are differences between patients who received treatment by homeopaths and those in the "No offer" group who would have received treatment had they been offered it.

** Effect size calculation: ES = M1-M2/SD1 (Kazis et al. 1989), using between group differences calculated using PP-analysis, divided by the baseline standard deviation.

PHQ-9: Patient Health Questionnaire. AD: Current use of antidepressants. >3LSC: More than 3 long-standing conditions.

Table 28. Anxiety outcomes at 6 months – Per protocol analysis

Baseline covariates controlled for	GAD-7 (n=396)			GAD-7, AD, >3LSC, PHQ-9, Employment, Age (n=369)		
	Mean (95% CI)*	p-value	Effect size**	Mean (95% CI)	p-value	Effect size**
Multiple Imputation	2.7 (1.4, 4.1)	0.000	0.59	2.3 (1.0, 3.7)	0.001	0.51
Regression Imputation	2.3 (1.1, 3.6)	0.000	0.51	2.1 (0.8, 3.4)	0.001	0.45
Last Observation Carried Forward	2.5 (1.2, 3.8)	0.000	0.55	2.1 (0.8, 3.5)	0.001	0.47
No imputation for missing data	2.4 (1.0, 3.8)	0.001	0.51	2.1 (0.7, 3.5)	0.003	0.44

* All results are differences between patients who received treatment by homeopaths and those in the "No offer" group who would have received treatment had they been offered it.

** Effect size calculation: ES = M1-M2/SD1 (Kazis et al. 1989), using between group differences calculated using PP-analysis, divided by the baseline standard deviation.

GAD-7: Generalized Anxiety Disorder Questionnaire. PHQ-9: Patient Health Questionnaire. AD: Current use of antidepressants. >3LSC: More than 3 long-standing conditions.

5.16.1 Comparison of ITT-, IV- and PP-analyses

Results result of the main IV-analysis (mean 2.6, 95% CI 0.5, 4.7) did not lie between the main ITT- (mean 1.4, 95% CI 0.2, 2.5) and the main PP-analysis (mean 2.3, 95% CI 0.9, 3.8). IV-analyses were better than both the ITT- and the PP-analyses. The same was true for all other analyses (also the anxiety outcome), whether using a method for imputation for missing data or not, and irrespective of which baseline outcomes that were controlled for (tables 20-21, 25-28). A comparison of ITT-, IV- and PP-analyses using MI for

imputation of missing data for depression and anxiety outcomes at 6 months is presented in tables 29 (Depression outcomes at 6 months – Comparison of ITT-, IV- and PP-analyses) and 30 (Anxiety outcomes at 6 months – Comparison of ITT-, IV- and PP-analyses).

Table 29. Depression outcomes at 6 months – Comparison of ITT-, IV- and PP-analyses

Baseline covariates controlled for	**PHQ-9**			**PHQ-9, AD, >3LSC, gender**		
	Mean (95% CI)*	**p-value**	**Effect size****	**Mean (95% CI)**	**p-value**	**Effect size****
ITT-analysis (n=458/456)	1.4 (0.2, 2.5)	0.019	0.30	1.2 (0.1, 2.4)	0.032	0.27
IV-analysis (n= 458/451)	2.6 (0.5, 4.7)	0.018	0.57	2.3 (0.2, 4.5)	0.031	0.52
PP-analysis (n=398/393)	2.3 (0.9, 3.8)	0.002	0.51	2.2 (0.8, 3.7)	0.003	0.49

* All analyses have been carried out using Multiple Imputation (MI) for imputation of missing values. Further descriptions are found under previous tables.

** Effect size calculation: ES = M1-M2/SD1 (Kazis et al. 1989), using between group differences calculated using IV analysis, divided by the baseline standard deviation.

PHQ-9: Patient Health Questionnaire. AD: Current use of antidepressants. >3LSC: More than 3 long-standing conditions.

Table 30. Anxiety outcomes at 6 months – Comparison of ITT-, IV- and PP-analyses

Baseline covariates controlled for	**GAD-7**			**GAD-7, AD, >3LSC, PHQ-9, Employment, Age**		
	Mean (95% CI)*	**p-value**	**Effect size****	**Mean (95% CI)**	**p-value**	**Effect size****
ITT-analysis (n=451/426)	1.5 (0.5, 2.5)	0.003	0.33	1.2 (0.2, 2.2)	0.019	0.26
IV-analysis (n=455/426)	2.8 (0.9, 4.8)	0.004	0.61	2.4 (0.4, 4.3)	0.018	0.51
PP-analysis (n=396/369)	2.7 (1.4, 4.1)	0.000	0.59	2.3 (1.0, 3.7)	0.001	0.51

* All analyses have been carried out using Multiple Imputation (MI) for imputation of missing values. Further descriptions are found under previous tables.

** Effect size calculation: ES = M1-M2/SD1 (Kazis et al. 1989), using between group differences calculated using IV analysis, divided by the baseline standard deviation.

GAD-7: Generalized Anxiety Disorder Questionnaire. PHQ-9: Patient Health Questionnaire. AD: Current use of antidepressants. >3LSC: More than 3 long-standing conditions.

These results suggest that one of the basic assumptions for carrying out IV-analyses was violated, as results suggested there was an effect of receiving the offer of treatment. Non-accepters, patients in the "Offer" group who did not take up the offer, "did better" than patients in the "No offer" group. An arising question is: How considerable is the effect of receiving the offer of treatment?

5.16.2 The effect of receiving the offer of treatment

Comparison of the results of ITT-, IV- and PP-analyses suggest that there was an effect of receiving the offer of treatment. A general linear model (GLM) was therefore used to compare results for non-accepters in the "Offer" group with results for "No offer" group patients. Analyses were carried out with and without methods for imputation of missing data, and controlling for baseline values, in the same way as for all ITT-, IV- and PP-analyses, both for the depression (PHQ-9) (table 31: Depression outcomes at 6 months – "Offer" group non-accepters compared to "No offer" group) and anxiety (GAD-7) outcomes (table 32: Anxiety outcomes at 6 months – "Offer" group non-accepters compared to "No offer" group).

Results showed only very small mean differences between "Offer" group non-accepters and "No offer" group patients. Results ranged from 0.1 (95% CI -1.6, 1.4, p=0.900) points to 0.7 (-2.3, 0.8, p=0.344) for the depression outcome, and from 0.0 (95% CI -1.3, 1.3, p=0.993) to 0.4 (-1.7, 0.9, p=0.551) for the anxiety outcome.

These results suggest there was no statistically or clinically significant effect of receiving the offer of treatment.

Table 31. Depression outcomes at 6 months – "Offer" group non-accepters compared to "No offer" group

	PHQ-9		**PHQ-9, AD, >3LSC, gender**	
	Mean (95% CI)*	**p-value**	**Mean (95% CI)**	**p-value**
Multiple Imputation	0.3 (-1.8, 1.2)	0.707	0.1 (-1.6, 1.4)	0.883
Regression Imputation	0.5 (-1.9, 0.9)	0.472	0.3 (-1.8, 1.1)	0.647
Last Observation Carried Forward	0.3 (-1.7, 1.2)	0.708	0.1 (-1.6, 1.4)	0.900
No imputation for missing data	0.7 (-2.3, 0.8)	0.344	0.6 (-2.1, 1.0)	0.461

* All results are differences between patients who received treatment by homeopaths and those in the "No offer" group who would have received treatment had they been offered it.

** Effect size calculation: ES = M1-M2/SD1 (Kazis et al. 1989), using between group differences calculated using IV analysis, divided by the pooled ("Offer" and "No offer" group) baseline standard deviation.

PHQ-9: Patient Health Questionnaire. AD: Current use of antidepressants. >3LSC: More than 3 long-standing conditions.

Table 32. Anxiety outcomes at 6 months – "Offer" group non-accepters compared to "No offer" group

Baseline covariates controlled for	GAD-7		GAD-7, AD, >3LSC, PHQ-9, Employment, Age	
	Mean (95% CI)*	p-value	Mean (95% CI)	p-value
Multiple Imputation	0.2 (-1.6, 1.1)	0.726	0.1 (-1.3, 1.3)	0.987
Regression Imputation	0.4 (-1.7, 0.9)	0.551	0.2 (-1.5, 1.0)	0.708
Last Observation Carried Forward	0.3 (-1.6, 1.0)	0.676	0.0 (-1.3, 1.3)	0.993
No imputation for missing data	0.0 (-1.4, 1.4)	0.983	0.2 (-1.2, 1.6)	0.783

* All results are differences between patients who received treatment by homeopaths and those in the "No offer" group who would have received treatment had they been offered it.

** Effect size calculation: ES = M1-M2/SD1 (Kazis et al. 1989), using between group differences calculated using IV analysis, divided by the pooled ("Offer" and "No offer" group) baseline standard deviation.

GAD-7: Generalized Anxiety Disorder Questionnaire. PHQ-9: Patient Health Questionnaire. AD: Current use of antidepressants. >3LSC: More than 3 long-standing conditions.

5.17 Comparison of outcomes for different practitioners

Separate analyses were carried out comparing differences in depression and anxiety outcomes between the seven practitioners providing the intervention in the trial. All analyses were carried out using the general linear model (GLM) with depression (PHQ-9) and anxiety (GAD-7) outcomes at 6 months. Only the main method (Multiple Imputation) was used for imputation of missing data in these analyses. Analyses were carried out using the same baseline covariates as in previous analyses.

Patients' mean 6 month PHQ-9 scores (estimated marginal means) between different practitioners varied from 10.2 to 12.8, with a between practitioner difference of 2.6 points, when controlling for baseline PHQ-9 scores only; and from 10.5 to 13.6 (difference 3.10) when controlling for all four baseline covariates. Between practitioner differences were however not statistically significant (p=0.980, 0.952).

Six month anxiety (GAD-7) scores ranged from 7.1 to 11.5 points (difference 4.4) when controlling for baseline GAD-7 scores only; and from 7.7 to 13.0 points (difference 5.3) when controlling for all baseline covariates. Results were not statistically significant (p=0.695, 0.376).

Results were not statistically significant as the differences were not large enough for the relatively small number of patients treated by each homeopath (range 6 to 15). In order for results to be statistically significant, each practitioner would have had to treat 11 times as many patients, with results similar as for the group of patients each practitioner treated (66 to 165 patients each, p=0.034). Ten times as many patients would give a p-value of 0.053 (data not shown).

5.18 The effectiveness of treatment by homeopaths in depression: Summary

Results of the main (ITT) analysis of the offer of treatment provided by a homeopath for patients with self-reported depression at 6 months suggested a between group difference of 1.4 (95% CI 0.2, 2.5, p=0.019) points for the depression (PHQ-9) outcome, and 1.5 (95% CI 0.5, 2.5, p=0.003) points for the anxiety (GAD-7) outcome, in favour of the "Offer" group. This gave a small effect size (*d*=0.30/0.33). The main IV-analyses showed a difference of 2.6 (95% CI 0.5, 4.7, p=0.018) points on PHQ-9 and 2.8 points (95% CI 0.9, 4.8, p=0.004) points on GAD-7, in favour of patients who received treatment by a homeopath, with a medium effect size (*d*=0.57/0.61).

Secondary analyses gave similar results, although some tests were not statistically significant, mostly for ITT-analyses. All results had wide confidence intervals, precluding any firm conclusion from being drawn.

6 Qualitative study: Depressed patients' experiences with treatment provided by homeopaths

The semi-structured interview study was carried out to explore what patients with self-reported unipolar depression experienced during and after treatment provided by homeopaths as an adjunct to usual care.

6.1 Selection and recruitment of patients for qualitative interviews

As the aim of the qualitative study was to explore depressed patients' experiences with homeopathic treatment, only patients who had received treatment by a homeopath were selected for interviews. A purposive selection was made in order to obtain views from patients with different baseline characteristics. It included patients of both genders, different age groups, with different degrees of depression and treated by different practitioners.

The interview guide developed prior to the study for the first and the second interview included questions about the consultation with a homeopath and taking a homeopathic medicine. Patients were asked whether there were similarities or differences when comparing homeopathy consultations and homeopathic remedies with antidepressants and other treatment they had received in the past. All patients invited for interviews therefore had current or past experience with using antidepressants or other depression treatment.

Individuals who were eligible for inclusion in the qualitative interview study were sent the letter with the invitation to participate and the consent form to be signed and returned if they agreed to participate. A researcher (PV) called patients, at the earliest 3 days after sending the letter, in order to give patients time to consider the invitation.

Out of 47 patients who were invited, 33 agreed and were interviewed. Sixteen interviews took place 1-2 months after patients' first consultation with a homeopath, and 30 interviews took place after about 6 months. Thirteen out of 33 patients were interviewed twice, whereas 17 were only interviewed at 6 months and three only at 1-2 months.

Out of the 14 patients who were invited, but who were not interviewed, five agreed to participate but later cancelled, three declined the invitation, three were indecisive, two agreed but did not turn up for the interview and one could not be reached.

6.2 Characteristics of qualitative interview patients

Out of 33 interviewed patients, 18 (54.5%) were female. The mean age of interviewed patients was 53 years with most in the age groups from 50-59 years (n=13, 39.4%) and 40-49 years (n=8, 24.2%). The remaining were 20-29 years (n=2, 6.1%), 30-39 years (n=3, 9.1%), 60-69 years (n=4, 12.1%), and 70-79 years (n=3, 9.1%) of age.

About two thirds of those who participated in interviews were from Sheffield (n=21, 63.6%), and about one third (n=12, 36.4%) were from Rotherham (n=6), Barnsley (n=3) and Doncaster (n=3). Half of the patients (n=16, 48.5%) were employed (unemployed n=16, unknown n=1). More than two fifths (n=15, 45.5%) lived in the most (n=12) and second most (n=3) socio-economically deprived areas, and over two fifths (n=15, 45.4%) in the least (n=4) and second least (n=11) deprived areas.

Patients treated by all seven homeopaths were interviewed. For logistical reasons, a higher number of interviews were carried out with patients who had been treated by homeopaths who saw a larger proportion of patients and who practised in Sheffield.

The mean baseline depression score (PHQ-9) was 16.5 (SD 4.6) for interviewed patients, which was comparable to patients who were treated by homeopaths, but not interviewed (16.1, SD 4.5). Depression scores for interviewed (11.3, SD 7.0) and non-interviewed (12.0, SD 6.9) were also comparable at 6 months.

Patients were divided between the three depression categories with 15 moderately (45.5%), eight moderately severe (24.2%) and nine (27.3%) severely depressed (unknown for one patient). Two out of three patients were taking antidepressants at the time of the interview and 93.9 % had used antidepressants in the past. Overall interviewed patients were taking 3.7 (SD 3.7) different types of medicines (for both mental and physical health problems).

The mean baseline anxiety score (GAD-7) was 13.7 (SD 5.4), which was similar to those who were not interviewed (12.8, SD 5.4). Those interviewed had slightly higher anxiety scores at 6 months (9.7, SD 6.0) compared to those who were treated by homeopaths, but not interviewed (7.2, SD 6.2), although differences were not statistically significant (p=0.10). Most patients were at baseline severely anxious (n=15, 45.5%), nine were moderately anxious (27.3%), six mildly anxious (18.2%) and one was not anxious at all (3.0%) (unknown n=2).

At baseline, interviewed patients had an average of 2.72 (SD 1.61) long-standing conditions (not interviewed 3.04, SD 1.80) and their BMI score was 27.40 (SD 4.35), comparable to those who were not interviewed (28.27, SD 6.77).

Compared to other patients who were treated by homeopaths, interviewed patients had comparable PHQ-9 and GAD-7 scores at baseline and 6 months, comparable numbers of long-standing conditions and BMI scores, were of a similar age, and were similarly distributed with regards to gender, employment and deprivation status. A larger proportion of interviewed patients were from Sheffield and fewer from Rotherham, compared to those who were not interviewed. This was mainly due to practical reasons, as it was more practical to carry out interviews in Sheffield, where the researcher (PV) was based. Moreover, interviewed patients were much more likely to currently be taking antidepressants or to have taken such medicines in the past. The reason for this was that an inclusion criterion for qualitative interviews was that patients should have experience with conventional medication or other conventional depression treatment, in order to facilitate comparison between this treatment and treatment provided by homeopaths.

In summary, qualitative interviews were carried out with a variety of patients, of both genders, different age groups, from different cities and deprivation groups, and were treated by different homeopaths. Both employed and unemployed patients were interviewed. Their depression and anxiety scores were similar to trial patients who had not been interviewed, both at baseline and 6 months. A higher percentage was currently taking antidepressants, compared to trial patients who were not interviewed, and almost all had taken antidepressants in the past.

6.3 Description of the qualitative interviews

A total of 46 interviews were carried out with 33 different patients. Interviews were audio-recorded using a digital voice recorder (Olympus VN-713PC) and lasted for an average of 55 minutes (median 51 minutes), ranging from 27 to 119 minutes (IQR 41-63), adding up to a total of more than 42 hours of interviews. Interviews mostly took place in the clinics where patients had received treatment by a homeopath, including Wellforce Integrated Medicine Centre in Sheffield (n=25), Clifton Medical Centre in Rotherham (n=7), Chapman Physiotherapy in Doncaster (n=6) and Western House Consulting Rooms in Barnsley (n=5). Two interviews were carried out over the internet, using Skype technology, and one took place at the School of Health and Related Research at the University of Sheffield.

6.4 The interview transcripts

With two exceptions, all audio-recordings were transcribed by Linda Pitt, a professional who has carried out interview transcriptions for Universities and market research for 20 years. Transcriptions were checked by one researcher (PV) and any discrepancies in understandings between the transcriber and the researcher were checked by a second researcher (PF or FTK). One of the remaining two interviews was transcribed by the researcher (PV) and checked by the professional transcriber (LP). In the last interview the audio-recording equipment failed. In this case the patient checked the researcher's interview notes and made corrections and additions.

Out of 974 pages of transcripts and more than 320 000 words, a total of 341 differences in understandings between the transcriber and the first researcher were identified. All but two differences were resolved in agreement with the second researcher. For the two remaining differences the third researcher was consulted and a majority vote was made.

6.5 Coding and analysis of interviews

The data corpus consisted of two sets of data resulting from the interviews shortly (1-2 months) after the first consultation with a homeopath, and interviews after a minimum of two follow-up consultations, about 6 months after the first consultation.

One researcher (PV) coded all transcripts. All statements considered relevant in answering the research question and the questions raised in the interview guide were coded. A total of 2,003 statements were coded. A second researcher (CR) checked a random selection of transcripts and found them to be appropriately coded.

No new issues adding information to the developed themes were identified during the last three interviews (interviews 14, 15 and 16) carried out 1-2 months after patients had started their treatment with a homeopath. It was therefore decided not to carry out any further interviews 1-2 months after patients' first consultation with a homeopath, but to continue with interviews at the second stage of interviews, 6 months after patients' first consultation. During the second round of interviews (at about 6 months), new issues were identified and new codes developed for each new interview contributing to further development of themes. The maximum, a total of 30 interviews, was therefore carried out at this phase of the study. This brought the total to 46 qualitative semi-structured interviews, carried out with 33 different patients.

For interviews carried out 1-2 months after treatment start, 129 codes based on patients' statements were initially developed. Revision of codes and quotes resulted in reduction to 110 codes. For interviews carried out at about 6 months, 126 codes were initially developed, and later reduced to 118 codes.

Most of the codes developed on the basis of qualitative interviews directly answered the research question on depressed patients' experiences with treatment provided by homeopaths. This included their experiences with the ***consultations*** with homeopaths, their experiences with ***taking homeopathic remedies***, the ***development of their state of health*** during the treatment course, and their ***knowledge, beliefs*** *and* ***understanding*** of the treatment after having received treatment for about 6 months. Themes were developed for these four areas.

In addition, patients also described their experience and understanding of ***depression and health issues***; their ***knowledge, beliefs and understanding of homeopathy*** prior to and at the onset of treatment; as well as their ***expectations***, ***hopes*** **and** ***attitudes*** with regards to the intervention. A number of ***issues*** were developed on the basis of this information (table 33: Qualitative interview study – Issues prior to and at start of treatment). This information was not termed ***themes***, but ***issues***, as they did not answer the main research question and they were not the main focus of the research. Nevertheless, it provided an insight into patients' "starting point", which formed a basis for understanding the context of the research and for understanding changes in patients' knowledge, beliefs and understanding from the start of the study and until the 6 month interview.

Although there were both male and female patients, the majority were female. Moreover, six female homeopaths and a single male homeopath were included in the project. Therefore, in the following sections, the female gender will consistently be used when referring to patients and homeopaths.

6.6 Understanding and experience of depression and health issues

Patients described what it feels like being depressed, their experience of taking antidepressants, their understanding of the causes of depression, and how they were coping with it. Results are also presented in table 33 (Qualitative interview study – Issues prior to and at start of treatment).

The ***feeling of depression*** was described in many different ways including having *lost the feeling of joy, pleasure* and *enthusiasm*, *going down*, *falling apart* or *crumbling*, *feeling miserable, feeling dark and lonely*, *having nothing to look forward to, feeling everything is pointless,* or *feeling indifferent* or *having no feelings at all*. Some described it as *having a black cloud above* or a *black dog on your back,* feeling *as if in a fog or a box,* as *a shroud over the brain,* and being *unable to see clearly*.

> *"When you are depressed you feel as if you've got a black cloud over you all the time." (I5)*

"It's like being in a little black box in prison. I call it Black Dog months. It's like having a black dog on your back." (I9)

Table 33. Qualitative interview study – Issues prior to and at start of treatment

Issues*	Patients' descriptions
Understanding and experience of depression and health issues	
Feeling depressed	Depressed, lack of joy, pleasure and enthusiasm; indifference; lack of feelings; feeling dark and lonely; nothing to look forward to; everything is pointless; black cloud above; black dog on your back; as if in a fog or box; shroud over brain; unable to see clearly
Isolation and inertia	Inability to carry out daily routines
Self-harm	Harming themselves; thoughts and plans of suicide
Accompanying symptoms	Anxiety; irritability; low self-confidence; feeling worthless; loss of energy; reduced appetite; sleep difficulties; physical symptoms
Uncertainty about depression	Uncertain whether being depressed
Antidepressants	Helped; uncertain if helped; no benefit; side effects; reluctance about and desire to discontinue antidepressants; withdrawal symptoms
Causes of depression	Stress; imbalance in brain chemistry; personality traits; physical disease; weather or season; unknown
Sense of control	Feeling of being in control; feeling of being controlled by external circumstances; coping mechanisms
Knowledge, beliefs and understanding of homeopathy	
No knowledge	Didn't know anything; don't know what it is
Assumptions	Chinese medicine; tonic; natural treatment; plant based; no synthetic chemicals; little risk; healthier than conventional treatment
Knowledge	Principle of similars; dilution of remedies; holistic
Credibility	Not heard any criticism; criticism in the media and elsewhere; positive testimonials
Expectations, hopes and attitudes	
Low expectations	No expectations; little expectations
Helpfulness (expectations)	Improvement; cure; discontinuing antidepressants; increased self-awareness
Improvement (hopes)	Improvement in mental state of health; discontinuing antidepressants; uncertainty about hopes; unreasonable hopes
Open-minded and positive	Open-minded; positive attitude towards treatment; must give it a try; avoiding information critical to homeopathy; neutral/unbiased starting point; believing in the treatment; most important whether improve and not why
Altruism	Helpful to others

***** Issues developed on the basis of patients' descriptions at 1-2 month interviews

Several patients described a tendency to ***isolate themselves*** and ***feeling inertia***, with *inability to carry out any daily routines*.

"You just don't look forward to anything. […] You have to force yourself to do things. […] You just feel miserable and nothing gives you any pleasure. […] It's like everything is in a cloud and a fog […]" (I7)

"I have grey days now. I don't have black days like I used to. But you wake up in the morning and there is this heaviness, this big cloud, this black mist or greyness now hanging over you […] I was just like a zombie. I just couldn't do anything. […] When you are feeling really bad, you don't want to be with anybody, anyway. You want to be on your own. You want to bury yourself in a hole sometimes and hide from the world." (I12)

"It's horrible when you are depressed. You don't want to see anybody. You don't answer the telephone. You don't answer the door. You just keep to yourself and that's it. […] You don't take any notice of anything and you don't laugh at anything. You just don't feel anything. You want to be shut away from everybody." (I25)

Several patients described having felt so depressed that they were ***harming themselves*** or thinking about or planning ***suicide***.

"I had been suffering with anxiety and depression for a number of years. It's gotten worse over the last couple of years. In the last few years, that's when I've been injuring myself." (I24)

"At your worst, you think about ending it and taking tablets and things." (I25)

"When I was at my lowest, I contemplated suicide on a few occasions." (I6)

Some patients were however ***uncertain*** as to whether they were depressed. As one patient said:

"I'm not sure if it was depression. If you define depression as kind of feeling down for sort of no reason than I think there were reasons for feeling quite fed up and I think a lot of it was grief and also physical response, because of hormones. […] I've probably been a bit susceptible to low mood throughout my life, very low level, low mood and not, people wouldn't necessarily know, because you kind of put on a brave face on things all the time and appear jolly in front of people." (I11)

Feeling depressed was also linked to ***other mental, physical or general symptoms***, such as *anxiety*, *irritability*, feeling *loss of energy*, *reduced appetite*, *loss of sleep* or *sleeping more than normally*, or experiencing different *accompanying physical symptoms*. Examples of statements illustrating this include:

> *"Reaction: bad temper, […] snappiness over the slightest little thing. […] I would snap at someone and I will be nasty and then I withdraw into myself and my wife said, sometimes I won't talk to her for one or two days." (I6)*

> *"I would go for days without eating, eating properly. […] When I were really depressed, at the bottom of my cycle, I would waken up absolutely covered in sweat." (I8)*

Some patients also described how the feeling of depression was connected to *low self-confidence* and *feeling worthless*:

> *"I don't want to go out. I don't want to see people. […] Low self-worth. [You] see everything in black and white instead of in colour […] It's like a weight on your chest. […] You just feel miserable and nothing gives you any pleasure." (I7)*

> *"[When] I've felt really low that in itself makes me believe that I can't do things and I don't want to do things. [The] low mood is linked to the self-doubt." (I14)*

Patients also presented a variety of experiences with and thoughts about ***antidepressants***, with some patients feeling the medication *helped them*, others were *uncertain* as to whether there was an effect or felt they had *no benefit* or they experienced *side effects*. Examples of patients' experiences with antidepressants include:

> *"[The antidepressant] stopped me being so like morbid. […] I was just sitting in my chair at home and just very, very lethargic and just looking out into the distance and feeling extremely oppressed by dark feelings in my head and just generally like completely at a loss. Even though I had a very happy home life, I just couldn't help*

this depression. [The antidepressant] obviously helped me – it appeared to get me out of a zone."

"I don't know whether it's not doing anything or it is doing its job […] For me, when I take them it doesn't seem to alter anything. […] It might be that they are doing the job and that's why I don't notice any effect with them." (I31)

"But they affected me driving […] I was like a zombie. […] It were affecting my vision very badly. It was affecting me driving. I was falling to sleep at work. Just little things like that you know. It was affecting my appetite. I were just like, you are not yourself, you are just walking about in a daze all the time […]" (I38)

Several patients expressed feelings of *reluctance* with regards to taking or stopping antidepressants, some wanted to *come off antidepressants*, and yet others experienced *withdrawal symptoms* when they had tried to do so in the past.

"I have to have medication reviews. […] They have suggested to stop taking them or let's work towards doing that. I have always resisted that. […] my goal is not to be taking them […] they have tried to sort of like take me off them. I've got worried about whether I am going to go backwards." (I20)

"The GP wanted me to carry it on for longer, but I didn't want to carry it on for longer, because I knew you could get hooked on it. I wanted to try and go through it myself." (I26)

"I used antidepressants a long time ago, in 2000. It was horrible. It took nearly two weeks to get used to it, I felt dreadful each time took it in that time. […] I felt dreadful for two weeks, couldn't sleep properly. I took it for a total of 6 months. […] Foolishly I just stopped taking them, the withdrawal symptoms were appalling. I should have done it gently. I felt awful for two to three days, lying in bed." (I33)

Patients had different views on the possible ***causes of depression*** and most commonly some form of *stress* was mentioned. This could either be *stress at work*, *in family life*, the *loss of family and friends* or *divorce*.

"Ninety-nine percent of my depression is down to business. My wife always said, if business is going well, you are on an up. If it's going bad, you are on a trough. […] I can nearly pinpoint due to my business life when I'm going to be at my lows." (I8)

"[…] I lost two of my best friends. They both passed away. […] I started getting a load of stress again and I gradually went downhill […]" (I24)

But a number of other reasons were mentioned, including an *imbalance in the brain chemistry*, they considered it to be linked to their *personality*, *physical disease*, the *weather or season*, or they *did not know*. Examples illustrating such views include:

"I know now, it's an illness in your brain. It's your chemicals in your brain." (I3)

"Maybe it's just something we have in our personalities." (I7)

"The [physical] disease is making it a lot worse for me in that I can't do things I could do ten years ago. […] That's basically what […] made me feel depressed." (I6)

"[Depression] from December to maybe middle of March." (I9)

Many patients described a ***sense of control***, with either a *feeling of being in control* or a *feeling of being controlled by external circumstances*. Their sense of control or lack of control seemed to influence their mood. For both groups of patients, the degrees to which they felt were in control, seemed to vary in intensity and it was explained in different ways. Examples of the *feeling of being controlled by external circumstances* included:

"I think [the depression] was depending on what was going on around me. At the time I'd got, I moved house and I got a new job. I started my own business. I had a lot of stuff going on around that wasn't very self-affirming which aided my depression anyway." (I32)

"I think the stress of work was lifted, so I did start to feel better. […] I think this year I just lost a lot of pressure out of my life. It's helped to elevate my mood." (I18)

Some patients found that although there were *certain things they could not control*, there were *other things they could do* to improve their mood and state of health. *Feelings of being in control* also seemed to be linked to *coping mechanisms*. Patients used a variety of approaches in order to contribute to improving their mood and general state of health.

"I think I should be able to cope with things. That I should be able to deal with things myself. […] I just have a word with myself and say, there is nothing you can do, so you've just got to leave it […] What I need to do with myself and this is just a work related thing is to be more organised. […] I need to delegate more." (I10)

"I've always worried about things. […] Where I work is insecure. […] I can't control whether the government decide to continue to fund the work that I do. […] If the government decide to cut the funding I will lose my job and so be it, I will lose my job. I've lived before [the workplace] and I will live after it as well hopefully. […] My experience and skills mean that I stand a good chance of getting some work somewhere else. So that's what I mean by things that I can control. It's like the anxiety, there is certain things I can do to help to manage it, you know. That's what I mean by exercise and by having a routine and going to bed at reasonable hours […] I am grasping some control and my sort of like anxiety. I am trying to help myself." (I20)

"Eating healthy and keeping fit. Thinking positive. Finding lots to do. Finding lots of things to look forward to." (I1)

6.6.1 Summary of experiences of depression and health issues

In summary, patients presented a wide variety of experiences of ***feeling depressed***, with descriptions that seem to correspond to key points mentioned in depression definitions such as the one found in DSM-V (Table 1: Major Depressive Episode – Diagnostic criteria according to DSM-V). Patients did however provide a great variety of descriptions, which

gave better insight into how patients experienced their mood and health problems. Patients also reported a variety of experiences with taking ***antidepressants***, with some feeling the medication ***helped*** improve their mood and ability to function, while others reported that they were ***uncertain*** or experienced ***no benefits***, and/or described ***side effects*** following the use of such medication. Several patients expressed ***reluctance*** with either taking or stopping antidepressants. Although some wanted to ***come off antidepressants***, others had experienced ***withdrawal symptoms*** when doing so. Various forms of ***stress*** were mentioned as significant causes of depression, although several other reasons were mentioned and some did not know what had caused the depression. Another issue that came up during the interviews was patients' ***feeling of control*** of their life situation and mood, and ***coping mechanisms*** they could apply to contribute to improve their mood and overall state of health.

In the following section, patients' knowledge, beliefs and understanding of homeopathy prior to and at the start of the treatment period are explored.

6.7 Knowledge, beliefs and understanding of homeopathy at treatment start

Very commonly patients stated they had ***no knowledge*** about homeopathy prior to agreeing to participate in the trial and also after having had one or two consultations with a homeopath (table 33: Qualitative interview study – Issues prior to and at start of treatment). For example, on being asked directly about prior knowledge about homeopathy, one patient (I14) responded: *"I didn't know anything about it."* Another said: *"I'd heard of homeopathy, but I didn't know what it was." (I4)*

Other patients had ***assumptions*** about homeopathy, some of which were *more* and others *less accurate assumptions*. Examples of *less accurate or inaccurate assumptions* included: "*I thought it was something to do with Chinese medicine." (I28)* And: *"I just thought it might be a mildly helpful tonic that would give you a little health kick for a short time." (I44)*

A few had read something on the internet, heard about homeopathy in the media or from others, or had acquaintances who had tried it themselves. The level of knowledge about

homeopathy *varied considerably* and most patients seemed to be uncertain about this knowledge. Whether their statements may be considered to be more or less accurate is subject to discussion. Such issues included homeopathy being "*natural", plant based* and *not containing synthetic chemicals*:

> *"I thought they were plant – well I suppose a lot of them are plant based." (I2)*

> *"I would think the homeopathic one hasn't got chemicals in like the Citalopram. I don't know the ingredients." (I3)*

> *"I'd not read anything about it at all. I felt that it would be something that – more natural." (I5)*

This perception, of homeopathic remedies being plant based or "more natural", did for some seem to mean that they would present *little risk* or be a *healthier treatment option compared to conventional medical treatment*:

> *"I thought it was more, I know this is naïve, but I thought it was a more healthy option. […] Something that was good for your body." (I2)*

> *"[…] natural remedies, rather than drug centred remedies. […] There's the technological drug induced route and then there is homeopathy, green leaf tea route, the natural route." (I6)*

Others seemed to have more ***knowledge*** about basic principles of homeopathy and questions surrounding the therapy. In particular the "*principle of similars*" and the *dilution of remedies* were mentioned, but also issues such as homeopathy being a *holistic* form of treatment.

> *"[An article on the internet] was explaining about the like treating like principle. […] It made sense to me in the sense that vaccination makes sense or the exposure to small amount of something might help." (I11)*

"I knew about it being sort of a very dilute version of something, whatever it was that was supposed to just give your body a little nudge in the right direction. Erm, and then it's part of like a holistic approach to medicines […] About treating the whole body as opposed to just one particular lot of symptoms. […] You treat it as a whole rather than just targeting or you are feeling upset like they give you something for that. You feel there is a bigger picture, because everything is sort of working in conjunction within your body." (I45)

Although many patients stated they had heard *no criticism* of homeopathy in the media or elsewhere, others addressed issues relating to the ***credibility*** of homeopathy. Debate in the media as to whether homeopathy works was mentioned by some patients, although these patients seemed to have considered "both sides" of the debate, as illustrated by the following patient's statement:

"There is a lot of stuff on internet about it. Split 50/50. 50 percent of people saying, it's total rubbish, it's total bunkum. The only thing you are taking is water because it's diluted that much that there is nothing left on it. And then you read other side, where people say, this works so well that we recommend it to everybody and then the farmers saying they have had homeopathic cures given to the animals and it's worked. So there is no placebo effect there, is there. Cause an animal doesn't know what it's taking." (I43)

Other patients referred to *positive testimonials* following homeopathic treatment, which is likely to have contributed to their decision to take part in the research project.

"I have to say that the testimonials on [the homeopath's] website assured that it was probably going to be worthwhile my going." (I44)

"I had a friend who erm, her sister had eczema and she had a special cream from a homeopath and it's cured her eczema. You hear of people almost being miraculously cured with homeopathic medicine." (I2)

"Our old dog […] nearly died. The vet got to the point and he said, look, you can't do anything for him. There is nothing else we can do. Have you ever thought of

acupuncture or homeopathy? I said, I believe in it. You can't tell a dog that it's psychological. We went to a vet […] who specialises in homeopathy. […] Within a fortnight he was a different dog. He just started to come back. He was out walking again. He got his life back." (I12)

6.7.1 Summary of knowledge, beliefs and understanding of homeopathy at treatment start

In summary, although many patients ***knew nothing*** about homeopathy, others had ***assumptions*** about the treatment which were more or less accurate and which they felt more or less confident about. A few had ***knowledge and understanding*** of homeopathy that was more accurate. Some of the main issues that were raised by patients included the treatment being *natural*, suggesting it could be *harmless*; and issues contributing to *increased or reduced* ***credibility*** of the treatment.

In the following section, we will be looking at patients' expectations, hopes and attitudes prior to and at the start of the treatment period.

6.8 Expectations, hopes and attitudes at treatment start

Several patients stated that they had *no or very little expectations* and only very few presented any clear expectations in terms of results of the treatment (table 33: Qualitative interview study – Issues prior to and at start of treatment). Those who had expectations were expecting it to be ***helpful*** so they could *stop current antidepressants*, *gain improved self-awareness* or even be *cured*. When taking part in the trial patients had however all signed the consent form, which included an agreement to continue any standard medication as prescribed by their GP/specialist.

"My expectation was the homeopathic remedy would give me more insight." (I46)

"[…] my expectation were that if I took these homeopathic medication, I'd be able to stop taking my Citalopram." (I3)

"I have had such chronic depression in the past that I was very keen to think that I might be cured." (I2)

Very few did however have such expectations. Nevertheless, most patients had *hopes* for the treatment, hoping for ***improvement*** *in their state of health*, in particular *improvement of their mental state of health* and in some cases that they might be able to *stop taking antidepressants*. One patient responded on being asked about hopes: *"Just lift me out of this black place. If it did that, I'd be fine." (I9)* Others examples included:

"I wanted something to happen. I was seeking the pill that solves everything." (I33)

"I had hopes that maybe I could get to the bottom of it, of all this negativeness, negativity. Maybe be able to come off Amitriptyline." (I5)

Several patients did however express *uncertainty* as to what they could hope for, or they assumed that they had *unreasonable* hopes.

"I hope it does work, I hope it does something. Make me fit, make me healthy and make me happy. It isn't going to do that, is it? Wake up and want to do something instead of just existing. […] Get my drive back. Drive to do stuff." (I1)

"[…] to make me feel a little bit calmer inside, if that's possible. I mean it's not going to be a miracle drug, is it? […] I'd like it to take all my worries away, might be wonderful. It's not going to happen. You just have to be realistic. I think if it had some sort of calming effect on me, then I think that would make me feel better." (I10)

"I was quite interested […] whether she could ease the pain […] I was kind of reaching for the sky. I thought that [the homeopath] would say, I've got a magic potion. I think it will cure you. I know that's totally impractical, but that was the kind of – I've tried everything else. Homeopathy might be the one." (I6)

Irrespective of whether patients had expectations or not and whether they had high or limited hopes for improving their health, most of them had a fairly ***open-minded and positive attitude*** towards the offered treatment. An open-minded attitude here refers to

patients' openness to the possibility that the treatment could have an effect and that their state of health could improve. Examples of statements illustrating this open-minded attitude include:

> *"I thought about it in the past and I wanted to give it a go. And I think that was yes, I wanted to see if they could, that they could do anything for me." (I26)*

> "*I am still open minded. I want it to work." (I28)*

Such an open-minded attitude did for some contribute to the decision to participate after having heard *others benefitting* from homeopathic treatment. As one patient expressed:

> *"Erm, I can't remember anything specific I've read, but definitely I have had – I remember people talking. I've read certainly articles about people who have said it has helped. I would really like it to work." (I7)*

Open-mindedness was typically characterised by patients' *"give it a try" attitude*. Several pointed out that you won't know if it works for you before you've tried it.

> *"I think if it's going to help me I've got to give it a try and give it a chance." (I31)*

> *"Don't make an opinion until you have tried it. It's not good having an opinion about something you know nothing about. So until you've tried it, don't have an opinion about it." (I43)*

As part of this ***open-minded attitude***, several patients stated that they preferred to *not know anything* about the treatment beforehand. They did *not want to hear critical remarks* about homeopathy. Several patients were reluctant to hear anything negative about homeopathy, as they were concerned that such views might reduce the effect of the treatment. A part of this was the need for *believing* in the treatment. These issues are illustrated by the following patient statements:

> *"I don't really want to know because I don't want to prejudice my thoughts on it. I want to be positive rather than negative, because I am a big believer in attitude, as*

daft as it sounds. If your attitude is right, then you are half way to doing something." (I30)

"I don't tend to look at negative views. […] I would prefer to read the positives and in my own mind say, it might work this. I will give it a go, rather than read, people that say it's an absolute load of rubbish and don't bother with it, which is kind of a negative view. […] If I were reading something that was critical, I wouldn't read it any more. I wouldn't bother with it. I would read the positive view and in my mind think, I will give it a try and see if it works. […] I think having negative views is a way of losing hope […]" (I22)

"[…] there is an element of faith in there. You have to have faith in the person to take the elixirs." (I16)

"[…] it could work for some people and not others. It depends what you are taking, really. Everyone is different. [It could work for] probably people who want it to, who want it to happen." (I1)

Although going for treatment is likely to involve some degree of hope of improvement and therefore to some extent a belief that the treatment might improve their health, some patients expressed their wish to have a more *"neutral" or "unbiased" starting point*. They did not want to receive any negatively loaded information about homeopathy, nor did they wish to hear anything positive. The following quotes illustrate such viewpoints:

"I didn't really want to know – I came into it with an open mind. I didn't know anything about homeopathy. She asked me if I wanted it explained. I said, no, I'd rather not know. I'd rather, it kind of felt that if I knew it would almost prejudice it. […] I wanted to keep an open mind and not have any, if you like, influences on it. […] I went in with positive attitude. […] I'm willing to try anything. […] Coming into it positive. If I walked through that door and thought, it's a load of crap this. What can it do? It can't do that. Then it can't work. I also think the same with Fluoxetine." (I8)

"I'm not sceptical about it. I'm not half full half empty regarding, I'm an equilibrium. […] I try not to jump to conclusions." (I21)

"She's given me leaflets, but to be honest I haven't read them. […] I didn't want to have any preconceived ideas. I wanted to just come into it and if it worked it worked. Brilliant, I wanted it to work, because I desperately wanted to get better. (I36)

It did not seem to matter to the patients whether there was a scientific rationale for the treatment. Most important was *whether patients improve, not why they improve*, illustrated by the following two statements:

"I've heard it referred to as Snake oil or one that's not proper medicine and the NHS shouldn't be subsidising it, because it's not backed up by science. I've read a lot about the placebo effect. I think sometimes things work that you don't necessarily know why they work or it might not be immediately apparent why they work. I don't think that science knows everything yet." (I11)

"Maybe it has a bit of a placebo effect, but who cares." (I8)

Although patients commonly expressed hope that the treatment might help them, some also seemed to have an *altruistic* attitude, hoping it would be *helpful to others*, also motivating them to participate in the research project.

"If it can't help me, if I take part, it could help someone else. […] If this research can help other people, I will feel I've done something good." (I3)

"I did do it because I am all for helping any study or anything that anyone is carrying out. If I think I am helping someone, that's fine. I will do it. I thought well, it might help me at the same time." (I37)

6.8.1 Summary of patients' expectations, hopes and attitudes at treatment start

In summary, many patients seemed to have *no or very little expectations* with regards to the outcome of treatment provided by homeopaths. Nevertheless, most patients *hoped* their mood would ***improve***, although they were usually *uncertain* as to the extent and type of improvement they could hope for. In spite of any doubts they had an ***open-minded and positive attitude*** towards the offered treatment. *Believing* in homeopathy was mentioned as important by some patients and some did *not want to hear critical remarks* about homeopathy in order not to be negatively influenced and thereby reducing their hopes. Others wanted to keep as *neutral* a starting point as possible and did therefore not want to hear anything positive about homeopathy either, but rather just see what would happen. Patients did not express any desires to find out how or why the treatment could have an effect, but were interested in seeing whether it would have an effect. They just wanted to *give it a try*. In the event that they would not benefit from the treatment, some seemed to have *altruistic* motivations for participating in the study.

So far, we have looked at patients' understanding and experience of depression, their knowledge, beliefs and understanding of homeopathy, as well as their expectations, hopes and attitudes to the treatment, prior to and at the onset of treatment. This gives us an understanding of their thoughts and understandings at the onset of treatment provided by homeopaths. The next section explores the experiences patients with the treatment patients described, and their thoughts and understandings about these experiences.

6.9 Depressed patients' experiences with treatment provided by homeopaths

The themes that have been developed on the basis of qualitative semi-structured interviews to describe patients' experiences with treatment provided by homeopaths are presented in four separate sections:

- **Experiences with the consultation**
- **Experiences with taking homeopathic remedies**
- **Knowledge, beliefs and understanding of homeopathy**
- **Changes and lack of changes in patients' state of health**

Thoughts, feelings and experiences were collected after patients had received treatment provided by a homeopath for a period of about 6 months, after at least two consultations with a homeopath, and after taking homeopathic remedies. Some experiences 1–2 months after treatment start are also included in these sections, as patients were more likely to recall their initial experiences shortly after treatment start, rather than after 6 months. The information has been used to develop themes describing patients' experiences, feelings, thoughts, beliefs and understandings. Results are also presented in table 34 (Qualitative interview study – Patients' experiences with treatment provided by homeopaths). For the sake of clarity, themes are in text presented using ***BOLD, ITALIC AND SMALL CAPITAL LETTERS***, sub-themes using ***bold italic letters*** and codes further describing themes and sub-themes with *italic letters*.

Table 34. Qualitative interview study – Patients' experiences with treatment provided by homeopaths

Themes*	Sub-themes	Patients' descriptions
Experiences with the consultation		
Caring support	***Feeling listened to and understood*** ***Acceptance***	Homeopath showing interest; listening; being warm and friendly; taking time; being responsive and understanding; accepting; non-judgmental; respectful
Trust	***Sincere and committed*** ***Competent*** ***Independent person*** ***Safety and concerns***	Sincere; committed; genuine; honest; motivation and desire to help; thorough; persistent Competent; uncertain about competence Neutral; interested in listening; can understand; intention to help; not family and friends
Optimism		Homeopath seems optimistic; positive; encouraging; enthusiastic
Opening up and unloading		Telling their stories; feeling of unloading worries and concerns; burden off shoulders
Reflection and realisation		Reflection; realisation; thinking deeper; bringing back forgotten memories

6.9.1 Experiences with the consultation

Five themes were developed on the basis of patients' description of their experience with the consultations they had with their homeopaths. The five themes are ***CARING SUPPORT***, ***TRUST***, ***OPTIMISM***, ***OPENING UP AND UNLOADING***, and ***REFLECTION AND REALISATION***. The last two of the four themes were primarily a result of the first two themes. Each theme has sub-themes and codes which further describe patients' experiences.

CARING SUPPORT

CARING SUPPORT expresses the quality of patients feeling supported by the homeopaths, who they perceived as a person who was interested in them, who understood them and who cared about their health and wellbeing. This theme consists of two sub-themes, ***feeling listened to and understood*** and feeling ***acceptance***. Although there is some overlap where patients' descriptions in several cases describe both sub-themes, they do at the same time represent different qualities.

All patients described an experience of ***feeling listened to*** and many also expressed that they felt ***understood*** by the homeopath. The homeopath was perceived as *showing interest*, *listening*, *being warm and friendly*, *taking time*, *being responsive* and *understanding* the patient's problems. The homeopath *showing interest* for and *listening* to the patient was expressed by all patients in one way or another, as one patient very simply expressed: "*[She] seemed eager to listen and quite caring, you know." (I1)* These qualities and the fact that homeopaths were *taking time* to *listen* to patients are illustrated by the following statement:

> *"I found it very easy to talk to her. […] The homeopath, you immediately felt like there was all the time in the world to talk, which of course you never feel at the GP. So that's the biggest difference that you get. She said she's wanting to know me and know the whole picture and erm, needed to find out as much about me as she could and you know, as quickly as she could. Very patient. That was very different in that she had the time and she was obviously listening to me and asking pertinent questions. Maybe the simple process that the homeopath was writing down what I was saying, that made me feel listened to […] Looking at me. She touch typed as well […] If someone makes eye contact when they are talking to you, you just automatically know that they are listening […] The fact that she was looking at me intensely, listening and writing down what I was saying made it feel like she was taking really taking notice of me. That makes, just made me feel it easier to talk and talk about things that are quite difficult to talk about." (I7)*

As was also shown in this quote, the patient's understanding of the homeopath as listening, in part resulted from the patients' observation of homeopath's body language. This was also mentioned by several other patients, as illustrated by the following examples:

> *"She was listening. She were looking at me. Passing me tissues. […] She seemed to be a good listener. […] It thought it was very nice of her to ring me op and ask how I was. She is excellent at getting me to talk." (I3)*

> *"[She] nodded in all the right places." (I2)*

> *"[It's] kind of body language. It's the non-communication skills that you could feel. You can always tell that someone is listening to you, you know, the eye contact and things like that. […] I can see it's your eyes mainly. And not blinking a lot […] I can see you're interested in what I am saying to you. […] And sometimes leaning forward does it as well […] and sometimes it's kind of just a hand, a touch of the hand or something." (I26)*

Many patients compared the *time* they were given when consulting with their GP with the time given when seeing the homeopath. Several patients expressed dissatisfaction with the lack of time they had with their GP, whereas others were still pleased with their GP consultations or expressed their understanding for GPs time pressures. Irrespective of this, the experience of seeing a homeopath consistently resulted in patients seeming pleased with the possibility they were given to express themselves more fully, to be *listened to* and better *understood*.

> *"Normally, you go to the doctor and you would, they don't have a lot of time, because they have a lot of patients to see. [You] know there is a queue of people outside in the waiting room. You need to get things done, fast." (I11)*

> *"[GPs] have been very understanding. In the quarter of an hour that you are sort of allotted you can't really bare your soul. Whereas, when you are with [the homeopath], all this one to one and you know you've got a bit of time, then you can tell her exactly what you are feeling." (I5)*

"[The] short one brushing the surface of problems. The long one is kind of delving a lot deeper." (I6)

The homeopath was perceived as not just *taking time*, but also *being willing to listen* to what the patient has to say and hereunder that the homeopath would "tolerate" and both want and need to hear what that the patient had to tell.

"[The homeopath] is quite happy to sit there and just listen to any problems I am having. If [others] caused me any trouble […] I can tell it to [the homeopath] and she can just let it wash over her and it doesn't affect her." (I24)

"[She] has to get to know you. When she gets to know you she's got to find out what the problem is and why I overeat, why I vomit, why I'm depressed. So, that's yes, that's probably where the counselling comes into it. So, the first couple of sessions were more like getting to know me sessions, which were nice." (I36

The perception of the homeopath listening to patients was accompanied by a perception of the homeopath being *warm and friendly*. Some also mentioned that the premises where the consultation took place had a similar quality. This quality of being warm and friendly is exemplified by the following two patients:

"[The homeopath] is a really lovely girl. Very warm aura. […] Makes you feel at ease. Doesn't rush you and seems to have a lot of compassion […]" (I16)

"[The homeopath's] rooms were homely and comforting and warm and comfortable. […] She has all these natural posters around. She also has a box of tissues right by the desk and that was very thoughtful. She had a glass of water there for me. [She] was right next to me with her laptop. […] She was looking at me and she was friendly." (I44)

Patients also described homeopaths as *understanding* and *responsive*, giving patients feedback, and this often contributed to ***REFLECTION AND REALISATION***, which will be discussed in further detail later. The quality of being *understanding* is here understood as *understanding* the patient's problems at a more "intellectual" level and not as

understanding in the sense of being *accepting*, which is dealt with separately under the sub-theme ***acceptance***. *Understanding* and being *responsive* are exemplified by the following statements:

> *"She just gives you the opportunity to have a talk. She asks you how you have been and how you have been feeling and how you have been coping. She encourages you to sort of come out with and talk about what has been happening. You feel that she understands and she relates to what you have been saying, you get a certain amount of feedback I think from her. I have had counsellors in the past that have just sat there and said absolutely nothing, which to me doesn't help. (Laughs) They have not lasted long. You get a bit of sort of feedback from her. You feel that she understands […]" (I23)*

> *"She certainly picked up on things that I think probably influenced the way I feel now that I hadn't thought about and made connections. [She] asked me what I was scared of. I said the only thing I was really scared of was heights. I'm not good with heights at all. We talked about how I felt if I was on the edge of a cliff and that feeling is very similar to how I felt when I was having a panic attack or an anxiety attack. I hadn't linked the two together before." (I7)*

The second sub-theme which, together with ***feeling listened to and understood***, contributes to the theme of ***CARING SUPPORT*** – is ***acceptance***. Acceptance represents a quality of feeling accepted, as opposed to feeling judged. The patient perceived the homeopath as being *accepting*, *non-judgmental* and *respectful*. This understanding of the homeopath seemed to be evoked by both the homeopath's verbal and non-verbal communication with the patient, and was also connected to qualities already mentioned, including *showing interest*, *listening* and *being responsive*, as illustrated in the following examples:

> *"[I] found that to be a very good experience. It was very positive that her attitude was really, she kind of, I suppose welcoming and accepting. […] She took a bit of time and appeared interested in what I was saying. [She] was very accepting and she acknowledged what you were saying. She had the time to kind of acknowledge and really listen to what you were saying. […] I think reflected back if you'd been*

through a difficult time. [By] summarising and repeating elements and kind of summarising and putting it into her words […] she showed that she had actually had thought about what you had said." (I11)

"She didn't judge me or anything and she just listened. [You] could see she was erm, very compassionate. […] Body language. I could tell she was being very compassionate." (I3)

Patients described past experiences with other practitioners that illustrate the opposite, the experience of *not feeling listened to* and *not feeling accepted*. No patient described perceiving their homeopath in such a way:

"It's just an aura about [some people]. It's the way they are. I am sorry, I find it difficult to explain. You can speak to some people and they don't respond at all. The body language just shoves you away. They don't want to know you really. [If] they are very unresponsive to you, you can speak to them and erm, they are very dismissive when they speak back to you or else they just give you a dirty look. […] There used to be a doctor […] You couldn't go and talk to him about anything that was wrong. If you did he didn't really listen to what you were saying. Very dismissive of what you have got to say. They don't accept anything that you say. What they do listen to they are sort of shut you up and say you are being silly. […] You can't possibly know what he is talking about. That is people they think they are so above the ordinary people." (I25)

Feeling acceptance also comes from patients feeling the homeopath is *respectful*. The patient is given freedom to express what she wishes to talk about, and not inappropriately pushed to say or do things she does not want to. She feels she has a degree of control in the consultation, feeling free to say what she wants to, as well as to refrain from saying things she feels uncomfortable telling to the homeopath at the given moment in time. These issues are expressed by in the following statements:

"[You] do come across people that are not easy to talk to. They are not as open. Whereas, [the homeopath] is open but she's not prying. […] She leaves it up to you to talk. […] She is not digging into my business. She just lets me talk, so that – I find

it very easy to talk to her and to open up. I don't have to – I am not holding back." (I25)

"She asked questions and allowed me to give the answer. She never tried to probe into anything too deep. She would let me go as deep as I wanted to go and that was it. She didn't go digging deeper. She never forced me into giving any information, which made me feel a lot more relaxed. It made me feel like I could give her, tell her what I wanted." (I15)

"There is still control in giving answers, because I could have said I was fine. (Laughs) So even though she might have asked very intimate questions, personal questions and things like that, you still choose what you answer. So effectively you are still in control. [The consultations] have been a good way of being able to talk about how I am feeling to be able to address anything that's come up. And [the homeopath] tends to let me, like yourself, talk about whatever and then again into questions to, are they, steer me to get some questions she wants answered." (I27)

Such behaviour seems to contribute to patients feeling safe with the practitioner and thereby feeling free to openly discuss their problems. Some patients explained how they had experienced behaviour with other practitioners or consultants that they felt were disrespectful and at times even causing patients to feel hurt and upset.

"[A therapist] was determined I was never going to address my weight issues until I had addressed all the other issues. […] He was insisting on going down an avenue that I really didn't want to go down. […] I didn't want to go down that line […] It wasn't what I'd gone for. [Another practitioner said] we are going to learn forgiveness and we are going to forgive rapists and murderers and people who abuse children. […] I've never been so cross and so upset and so hurt and so angry. " (I12)

A few patients mentioned to their GP or other healthcare practitioner that they were enrolled in a research project where they received treatment provided by homeopaths. Healthcare practitioners' responses varied, with some instances where patients' choice to participate in the research project was *respected*, *accepted* and *supported* by their healthcare practitioner, and other cases where it was not. In situations where healthcare

practitioners did not support patients in their decision to receive treatment provided by homeopaths, this led to patients either ignoring the healthcare practitioner's remarks or withdrawing from that particular practitioner's treatment, as illustrated by one patient:

> *"[My] GP said to me, if it's not doing you any harm, keep doing it. My psychiatrist had a dicky fit. […] I said I was seeing [the homeopath], you know, and he absolutely went up the wall. He says, you can't do that. I said, why? He said because you are taking medication. I said, well, she has looked at – I have given her a list of all my medication and she says, the stuff she's given me is compatible with my medication and he said, no, it isn't. […] He then said, do you think it's about time [you] stop seeing me. I says, well, I says, to be honest with you, I am getting more out of [the homeopath] than what I get out of you. It might be a good thing to stop seeing you. He says, right, I will put it down that I have signed you off. […] I felt if that's the way they react, I don't think it's a good idea seeing them anyway. It didn't bother me that he threw me off. I thought, if that's his attitude then it's not going to help me anyway. [...] It was just negativity. From me telling him to me walking out, everything were just as though I shouldn't be there and I were wasting his time." (I31)*

Although no experience was reported of homeopaths being disrespectful, some found it difficult at first to open up and the consultation could be challenging, but all these patients expressed that this was a more transitional phase which was followed by a feeling that it had been a positive experience.

> *"[When] I first saw her, I was a bit anxious as I am normally with people. The second time I was very relaxed […]" (I16)*

> *"I cried, maybe cried over the first two sessions because I felt a little bit, I was embarrassed or a little bit ashamed of my feelings. The first two times I cried all the way through. […] At first, I just felt I was just ashamed with myself. I felt as if I'd let myself down. I shouldn't be like this. And then I remember walking out of here and thinking I feel more relief after that." (I26)*

TRUST

TRUST is the second theme developed which describes patients' experiences of consultations with homeopaths. It involves both trust of the practitioner – the homeopath – as well as trust in the treatment. ***TRUST*** involves four sub-themes, of which three describe what patients perceived important in homeopaths in order to instil a feeling of ***TRUST***, namely being ***sincere and committed***, ***competent***, and being an ***independent person***. The fourth sub-theme, ***safety and concerns***, describes issues that relate to both the homeopath and the treatment.

Patients described homeopaths as being ***sincere***, ***committed***, *genuine* and *honest*, with *motivation* and a *desire to help* them. The following statements illustrate these qualities:

> *"[This] programme feels very genuine. [It] just feels honest. That is what I think about it. You know, [the homeopath] seems very, very honest. She seems very sincere. I think she genuinely wants to help people." (I20)*

> *"[It's] one-to-one, face-to-face, you're important, they listen to you. I felt it was a similar experience talking to a counsellor, as talking to [the homeopath]. Whether that's her or the general experience of seeing a homeopath, I don't know. The focus is on the individual, it's about your condition, trying to help you. […] She has convinced me that it's there. I said I'm sorry if I'm a difficult patient, client. She says: Don't worry, we'll find it, we'll take as long as it takes. She said it not once, but at least twice, maybe three times. Her strength, continual, is that she will. She's determined." (I33)*

The last of the two statements also add the qualities of being *thorough* and *persistent*, which in part describes how homeopaths were perceived to being ***sincere and committed***. This involves posing searching questions, trying to get to the bottom of the patient's complaints, and keeping up the search for a treatment that may eventually be of benefit to the patient. It brings us again back to the issue of spending a considerable amount of time on consultations, as has been described before. Being ***sincere and committed***, and as part of this, being *thorough* and *persistent*, is further described by the following patient quotes:

"I didn't expect it to be as deep as what it is. I didn't expect it to go in so many avenues. I didn't think she would worry about the fact I've got a bad ankle or my fingers are getting a bit of arthritis and I've got arthritis and I thought she won't want to know about that. It will all be about the mental health part. It would focus on that. It doesn't, it goes into everything. If I've had a bad day, is there any reason why I had that bad day? Is there any things that made it happen. If I say I had a really bad week, she wants to know in what way I had a bad week. How it affected me and what I did to stop it being a bad week. I didn't realise the depth of the package that you get, which I think is a good thing." (I31)

"[The homeopath] said what we want to do is get you to a place where you don't just burst into tears and you don't rant and rave. So you're just on a nice even keel. She says but we need to assess you through this year and see how you go." (I27)

Most patients commenting on the homeopath's competence said they perceived her as being ***competent***, which contributed to their feeling of ***TRUST*** towards the practitioner and the treatment.

"She's brilliant. She really is, she knows her job doesn't she? […] I think she already knew what was wrong with me to 90 % and she tried the small tablet dose or something and then something else and then said, right, we will try these. I said, I get this constant pain in my shoulder. She showed me in the memos or whatever she has and she said, shoulder. I said, brilliant like. She is very good at her job. That is just my opinion. Other people might think different. You know what I mean. As I say, I think she picks up very well. […] She can pick it up very well. I saw her on three or four occasions and every time I walk through the door, she says, you are better. You are getting better. She knew, you see. She picks up really well. [She] seems to know her job." (I35)

"Seems to know her job. Knew what she was doing." (I9)

Some did however express some uncertainty with regards to their homeopath's competence.

"I didn't know how qualified he was in what he was doing." (I12)

The third sub-theme which contributed to patients' feeling of ***TRUST*** in the homeopath was the fact that it was an ***independent person***. This gave patients a greater feeling of freedom to express their thoughts and feelings, as they were not (or very little) concerned that the homeopath would be burdened by hearing the patient's problems. Patients reported not wanting to burden their *family members and friends*, or not feeling comfortable enough to tell others about their problems or thinking they would not understand. The homeopath, on the other hand, was someone who they considered more *neutral*, someone who was *interested in listening* to them, who *could understand* and who had the *intention of helping* them.

"It's helpful to be able to unload to someone that doesn't know you and is […] neutral. […] I've got one close friend and she knows me, she knows me inside out. I don't tell relations how I feel. They have got their own troubles. They don't want to be listening to me and [the homeopath] does." (I5)

"You can talk to somebody better that you don't know than confiding in somebody that you do know. […] I just felt a bit relieved, I suppose that I'd somebody to talk to. Tell her all my troubles. I can't tell [my husband] all my troubles. […] I don't very often talk to friends. Not about my personal life. I'm inclined to put a different face on it altogether." (I4)

"Being able to open up to someone, I think. Someone that you don't know, initially. Unlike talking to family or friends – I don't know, it's difficult to explain, really. But er, it's someone who listens to you and is trying to help you in that respect. […] It's like talking to someone who you have known forever. But, they are trying to help you, rather than not being a friend, but not being a friend or relation as such and you kind of explain how you are feeling at the time and they understand. Say that to your friend or relative and they probably won't understand." (I37)

The fourth sub-theme contributing to the feeling of ***TRUST*** is ***safety and concerns***. Experienced side effects of treatment are described later, in section 6.8.5 (Changes and lack of changes in patients' state of health), but patients also had other thoughts on the

safety of the treatment which could either reduce or improve the overall feeling of ***TRUST*** in the treatment. Issues of ***safety*** could be of ***concern*** to the patient, although ***concerns*** could also include issues not directly related to ***safety***. Many of the patients did not express any concerns regarding safety when speaking about their experiences. When asked directly, they generally responded that they had *no concerns* about risks or side effects of the treatment. Treatment was considered to be safe, natural and healthy. Some simply trusted the homeopath and others were reassured about their concern after checking with the homeopath or elsewhere, as illustrated by the following examples:

> *"I don't think she said anything about [any possible reactions]. I told [her] what I was on and I thought, she's not going to give me something that's going to damage anything. I had no worries." (I5)*

> *"[I was] checking is this safe to take also while I am breastfeeding. […] It's completely safe. I think I read somewhere there is no known side effects at all over any of the medication." (I38)*

> *"[The homeopath] assures me that there is no side effects and it won't – it's not detrimental to other medications I am taking that's been prescribed. So I'm taking her word for it." (I42)*

The main concern raised by patients was *lack of information provided by their homeopath* and patients did not feel they had asked the homeopath sufficient questions and therefore felt they had a *lack of understanding of the treatment*. (Note: The word "tapping" in the quote below refers to succussion (shaking) referred to in section 3.1: What is homeopathy?)

> *"[She] didn't say what the homeopathic medicine would help or whether it would help both or – so I don't really know erm, what to expect. […] I don't really know what I'm taking it for. […] I didn't ask enough questions. […] I should have asked about the contents of the medicine. […] I should have asked when I could have expected to see an improvement. […] I'm looking forward to my next appointment with [the homeopath] so that I can ask her about the contents of it and what it's for and the tapping." (I18)*

"We didn't talk much about the medication she was to offer. […] I'm not enlightened after speaking with [the homeopath] as to what homeopathy is. She talked about my condition, my depression, family life and things like that, but very little about what homeopathy was or what it would offer me. […] I perhaps should have asked a few more questions at the end. She did say, you know, have you any questions? I did ask one, the one I mentioned about what would you be centring the treatment on? Would it be pain or what have you? And erm, she didn't really answer that." (I6)

Other patients did on the other hand feel they had received *sufficient information* from the homeopath, as illustrated by the following patient statement:

"She explained what homeopathy was. [She] talked about the research that had been done and about how people or the person who really publicised it the most had tried to disprove it and found that you know, the research showed that these remedies did actually work. […] I knew that it was very dilute amounts of I thought natural products. I didn't realise that one thing that the homeopath said to me was that it caused a reaction similar to the symptoms that you are feeling […] A little bit about the history of homeopathy, which I found quite interesting. Erm, I think, you know, just made if sound more scientific than perhaps I had thought before. [She said] you will feel more positive and maybe be able to come off Citalopram eventually. I also have eczema, but I think possibly a symptom of stress. It certainly gets worse when I'm stressed. So she said that might get better and that I might sleep better." (I7)

Some patients found that some of the questions the homeopaths posed were strange. As explained in section 3.1 (What is homeopathy), homeopaths may use such information as part of their overall understanding of the patient. These questions did however not seem to make patients concerned about the treatment.

"The first consultation was two hours, being asked odd questions. Like: Do you like dogs? I can't recall if that was a question, but it was that kind of questions. What has that to do with my depression? It was interesting." (I33)

Some patients were concerned that the homeopathic remedies could have *side effects* and others that it might be a *placebo*. Concerns about side effects could arise from the name of certain homeopathic remedies, such as in the example below. In this particular case, the patient refers to the homeopathic remedy Arsenicum album, which is produced with the use of arsenic. However, these homeopathic remedies are diluted to such an extent in the product homeopaths prescribe for patients that they are unlikely to cause any side effects. Mostly, patients were reassured by the homeopath and in one case also by the patient's GP:

> *"I think I was so wound up by the fact that […] I was being put on arsenic. […] I found it quite frightening. In fact, I was quite frightened even starting taking it. I even mentioned it to my GP who again backed up what [the homeopath] had said about it. […] He was explaining about the memory with the arsenic. It's like the memory. It's not, you are not drinking loads of arsenic." (I12)*

> *"I thought it was going to be one of those like blind trials, so so many people get something and so many people get a placebo. Erm, I thought well, it can't hurt either way, which is why I thought it were something I'd like to take up. And then [the homeopath] said, no, everybody gets the stuff. [She] explained how it worked and because it was all natural, it shouldn't have many, if any, side effects. Because the doses were so small." (I45)*

As already explained patients felt listened to, understood and accepted. However, a few patients also expressed some concern about *being categorised*:

> *"[The homeopath] might have mentioned that the sort of classifications […] when I thought, these are all classifications of people written by Victorians who did some pretty weird things and had weird ideas about the world in lots of ways. It made me a bit more sceptical." (I11)*

> *"She keeps writing all the time and she's making lists and she said she'd arrived at the gold remedy based on some of the things that I had told her. […] The words I used were like "I blew him away", quite aggressive words but I can't remember the words specifically, but then she said typically people who are gold type would choose to die by jumping. That kind of freaked me out that you can sort of, not again we*

were back to categories and like, ticking boxes, but I understood [it's] much more of an open thought process of, what this person is that's in front of me, and that makes me feel valued." (I21)

OPTIMISM

OPTIMISM is the third theme developed to describe patients' experiences of consultations with homeopaths. Patients described homeopaths being *optimistic*, *positive*, *encouraging* and *enthusiastic*, thereby contributing to reassuring patients and increasing their hopes of improvement. These qualities are illustrated by the following statements:

"She listens a lot and tries to give you positive feedback I would say and tries to make you think what flooding the situation for a happy ending and not a sad ending. […] I don't know how she does it. […] I think if you have been feeling low for a long time it's hard to get back up. It's like having a best friend to talk to. [She's] very good at listening and making you see things in a different way, flipping things. Making you look at the positives instead of negatives, because I am a very negative person. I think she's helped me try and take the positive out of the negative and I think that with these tablets has helped, yes. [She] just really listens to you and engage with you and try and understand things and then give you some positive feedback." (I39)

"I think I am the sort of person who responds quite well to having some encouragement and a bit of someone I suppose that focusing on positive side of things and what the possibilities are rather than going back and analysing all the negatives and sort of going through analysing all the negative feelings because I think you get to a point with analysing feelings where you've said all there is say really and you know why you feel the way you do and you know that is natural and you should feel like that because otherwise you would be a machine. [It's] treating you as a person knowing what your history is but also being where there is some optimism in the future or in one way or another, so focusing on that as well. So yes, sort of looking forward a little bit too rather than just always just fixing this problem and this thing that's wrong." (I29)

"It's almost like an enthusiasm from [the homeopath]. When you tell her something and she asks something and then you get this sort of enthusiasm that she is pleased that you are progressing [...]" (I23)

Some homeopaths did however seem to have more moderately optimistic expectations for improvements in patients' state of health, which also affected patients' expectations for the treatment, as illustrated by the following statement:

"[The homeopath] has said to me, it's not a miraculous thing that happens overnight, it'll be, if you get, hopefully you will get benefits that will come steadily, step by step. I don't expect miraculous feeling, running up and down and shouting eureka." (I31)

OPENING UP AND UNLOADING

The first two themes developed on the basis of patients' description of the consultations, ***CARING SUPPORT***, and ***TRUST***, contribute to the fourth theme – ***OPENING UP AND UNLOADING***, Patients' expressed that ***feeling listened to***, ***understood*** and ***accepted*** contributed to them *telling their stories*, thereby resulting in a *feeling of unloading their worries and concerns.* However, patients would not necessarily do so right from the start. As already described under the theme of ***CARING SUPPORT***, patients could feel a bit *anxious or embarrassed* during the initial consultations and *opened up after a while*. Either during the first consultation or after having seen the homeopath a few times, patients developed a feeling of ***TRUST*** contributing to strengthening the relationship between the patient and the homeopath. Patients felt free to say what they wanted to say, feeling *relaxed* and having a sense of *being in control* of the consultation, without feeling pressured by the practitioner. These experiences of the consultations are summarised by a single patient who has not yet been quoted:

"I was a bit anxious about coming to see her. […] I didn't know what I needed to say or what she would need to know or anything. She was really easy to talk to so it got all off my chest. […] I felt like she had the time to listen to me, even she might not have wanted to, but I felt like she did (laughs) wanted to listen to me. Took it on board and understood me. […] I just didn't feel rushed. Anything she said, she just

made me feel at ease and I didn't feel like I needed to get out straight away being rushed or anything like that. [When] I get home it feels like I don't have to think about that problem anymore. I've have told someone so it's off my mind. [Once] I talk to her about something which I can't do at home it just feels like there is less pressure and there is less things in my head rolling around. Once they are out, I am not like I said, once they are out here and then I leave them like feel a bit like clearer and just a lot of pressure and weight off my shoulders and stuff." (I40)

Feeling listened to, ***understood*** and ***accepted***, contributing to ***OPENING UP AND UNLOADING***, and thereby getting some *burden off the shoulders* is also exemplified by the following patient's statement:

"Feels like a weight has been lifted off my shoulders. You can breathe again. You don't feel so suffocated to hear your thoughts. A huge weight off my shoulders I would say. I feel a lot happier person for having spoken to her." (I39)

The theme of ***OPENING UP AND UNLOADING*** is the first theme that describes what could be considered a therapeutic effect. Even though it could have a long-term effects, ***OPENING UP AND UNLOADING*** has been reported here and not under section 6.8.5 (Changes and lack of changes in patients' state of health) as it solely took place during consultations, whereas other changes took place either during and after consultations, or solely after consultations. It is nevertheless closely linked to some of the themes that will be presented later, thereby also providing an insight into how themes in the different sections are linked together to describe the overall experience patients described.

REFLECTION AND REALISATION

As explained in the previous section, patients' experience of ***CARING SUPPORT*** and ***TRUST*** contributed to them ***OPENING UP AND UNLOADING***. While patients said they ***felt listened to***, most also described being posed questions and receiving comments from homeopaths that made them *think more and deeper* about their healthcare issues, *bringing back forgotten memories*, in short – it contributed to ***REFLECTION AND REALISATION***. They ***REFLECTED*** on their healthcare situation and their current and past life situation. And this process of ***REFLECTION*** led to a number of ***REALISATIONS***, as illustrated by the following statements:

"I found the interview with [the homeopath] quite good in a lot of respects in that it, the questions she were asking were quite good and led me into various, perhaps I've not touched before about how depressed I was, what was causing that depression and what I'd done to try and stop the causation of depression. [There were] chains of questions and she did tend to do that, you know, once I'd answered a question, she would ask a follow up question and then another follow up question. Each one delved a little deeper, I think, which I found interesting, because it was making me think about things that I'd perhaps never thought about before." (I6)

"I think sitting and talking to [the homeopath], and [she was] making me realise that where is my anger triggered, where is the anxiety triggered from. How is it triggered? What is making me triggered? What is making me feel anxiety filled? What am I not dealing with? What else am I taking it from work as well as? So it wasn't just only about taking the remedies but having, [the homeopath] kind of let me look at things and saying, well, how do you get work and life balance. [When the homeopath] and I first started talking, it was about I had to do what external forces wanted to do. So I had to do what work wanted me to do and I had to please the work and I have to please everybody else, that's my feeling. I have to go with it. And then taking the remedy have made me realise, yes, I am anxiety filled and I live with anxiety. […] So I was there trying to please. where really to be honest, I don't really need to please, I just need to do what is right for me and if it is not right, then find out what is right for me, and that's what I've learned as well. [The] remedy made me kind of realise that I don't always need a tablet to fix it. And I mean, antidepressant, I mean a chemicalised tablet to fix it. Maybe I just need to understand about me, but the workings of my mind, the way I react to things and things like that. And I think that's what [the homeopath] has helped me understand about me and the remedy. [It's] been a learning curve. I've enjoyed it. I've loved it. It's made me kind of, reflect on. And I think if I'd not met [the homeopath] and the remedy, I don't think I would have made the decisions I have made. I think I would have been still battling trying to find a conclusion to why I feel anxiety filled, why do I feel depressed. I'll always feel the way I did about my employees because of the situation that happened to me. I can't change human behaviour, it's just the way it is, so I can work with that or step away from that, whatever is best for me. And that's how I feel and I think,

well, you will get some people do it that way and you just have to accept it and not let it ride on you, which is very difficult. I don't think people are ever taught that you can't change human nature and that person just that way and there is nothing you can do about it, no matter if that is that person, the only thing you can change is the way you react to that person." (I41)

"What was great as well was talking to the homeopath. I kind of realised how much I'd been through. [It] was much easier and it was my first experience of clearly describing my experience to someone else. Ehm, and that had a very positive effect, because it felt like I assimilated my experience a little more. And I noticed that talking in detail about my fears wouldn't set me off. It almost made me realise when I was talking about my fears and my experiences to her, actually was very safe, and I wasn't having any thoughts or fears coming up. [I] wanted to gain understanding from it, as well as recover psychologically, but I felt the recovery was gaining a better understanding of myself. […] And so I've gained a kind of understanding ehm, but also a sense of security. That means I can feel anxious or low or slightly depressed or feel very well, but um, it doesn't have such an overwhelming impact on myself. I'm not worried about removing all anxiety." (I46)

As these patients described, the treatment with a homeopath, and in particular the consultations, led to a process of ***REFLECTION AND REALISATION***. Patients could take this improved insight and these ***REALISATIONS*** with them into their everyday lives. This could in turn positively influence their mental health and overall sense of wellbeing, which is discussed in section 6.8.5 (Changes and lack of changes in patients' state of health).

Summary of patients' experiences with the consultations with a homeopath

In summary, the five themes developed on the basis of patients' descriptions of their experience with the consultations with homeopaths are ***CARING SUPPORT***, ***TRUST***, ***OPTIMISM***, ***OPENING UP AND UNLOADING***, and ***REFLECTION AND REALISATION***.

Patients described ***feeling listened to*** and *understood* as homeopaths were perceived to *listen* to them, *showing interest* in them, being *warm and friendly*, giving patients sufficient *time* to describe their thoughts, feelings and experiences, and being *responsive* to patients.

Patients felt ***accepted***, *valued* and *not judged*. This all contributed to development of the theme ***CARING SUPPORT***.

Furthermore, qualities were described contributing to the ***TRUST*** patients developed in their homeopath. Patients perceived the homeopath as being ***sincere and committed***, *thorough* and *persistent*, trying to get to the root of the problem and not giving easily up in the pursuit to help patients. It was also considered important that the homeopath was an ***independent person***, a *stranger*, rather than a family member or friend. This contributed to patients feeling comfortable with sharing their problems with the homeopath, trusting the homeopath. But the *stranger* could not be "just anyone", but should be someone who is perceived to be ***competent***. Mostly patients had no or only minor ***concerns*** about the homeopath or the treatment. However, some issues may have contributed to reducing their ***TRUST*** in the homeopath and the treatment. The most prominent issue was *lack of information* about homeopathy, in particular about the homeopathic remedies and about what patients could expect.

OPTIMISM was described as the homeopath being perceived to be *optimistic*, *positive*, *encouraging* and *enthusiastic*. This contributed to increasing patients' *hopes* for the treatment.

The theme of ***OPENING UP AND UNLOADING*** seemed to result from the first two themes, ***CARING SUPPORT*** and ***TRUST***. The experience of the consultation contributed to patients feeling supported by a caring practitioner in whom they also had developed a sense of ***TRUST***. Many patients explained that they rarely open up to others and talk about themselves and their life situation and healthcare problems, and some said they never before had told anyone as much as they told their homeopath.

> *"I must feel comfortable with her to have told her some of the things I've told her. The things that I have never told anyone." (I30)*

The final theme describing patients' experiences with the consultation with homeopaths was ***REFLECTION AND REALISATION***. The questions posed and comments made by homeopaths during consultations contributed to patients *thinking deeper*, *remembering things* they had not thought about for a long time, and coming to ***REALISATIONS*** about their

lives, their healthcare situation and how they could contribute to changing their state of health and wellbeing.

This brings us on to the section describing patients' experiences with treatment provided by homeopaths – experiences with taking homeopathic remedies.

6.9.2 Experiences with taking homeopathic remedies

Patients' descriptions of their experiences following homeopathic treatment are described in section 6.8.5 (Changes and lack of changes in patients' state of health), whereas their understanding of how the treatment works are described in section 6.8.3 (Knowledge, beliefs and understanding of homeopathy). Other experiences patients had with taking homeopathic remedies involved the ***FORM AND AMOUNT OF HOMEOPATHIC REMEDIES***, and the ***PROCEDURES FOR TAKING HOMEOPATHIC REMEDIES***. Results are also presented in table 34 (Qualitative interview study – Patients' experiences with treatment provided by homeopaths).

Table 34. Qualitative interview study – Patients' experiences with treatment provided by homeopaths (continued)

Experiences with taking the homeopathic remedies		
Form and amount of homeopathic		Small sweet pills; liquid remedies; single or daily doses
Procedures for taking homeopathic remedies		Dissolved in mouth/under tongue; avoid touching remedies; dissolve remedy in water; take apart from food and drinks; avoid certain substances; drink water; strange and difficult

Patients' descriptions of the ***FORM AND AMOUNT OF HOMEOPATHIC REMEDIES*** suggest they were given either *small pills* or *liquid remedies*. Some described taking a *single dose* of a *small pill* which *tasted sweet*, sometimes taken in *daily doses* of the homeopathic remedy. Others were given *liquid remedies* which commonly were *taken on a daily basis*:

"I just took the one tablet." (I4)

"It's a brown bottle with a dropper in it. [You take] five drops in an ounce of water every morning." (I32)

"I wouldn't say size of a pea, to be honest with you. It was tiny. Only that big. It's really small. […]"And then it says not to touch it and try and work it up to bag and just let it dissolve under your tongue. I think it's 15, 20 minutes after don't drink or eat anything. I took that. It says to avoid strong coffee and mint, which I found strange." (I8)

The ***PROCEDURES FOR TAKING HOMEOPATHIC REMEDIES*** consisted of how to take the remedy. Pills were to be *dissolved in the mouth or under the tongue* and as shown in the example above, some patients were instructed to *not touch the homeopathic remedy*. Drops were to be *dissolved in water*. Some patients reported that the remedies were to be *taken apart from food and drinks*, and some were given instructions on certain *substances to avoid*, whereas one homeopath's patients were commonly *recommended to drink water*, as seen in the following example:

"You put [the homeopathic remedy] under your tongue. […] And it just dissolves. […] It works with water. You have to drink lots of water and it is just helping and balancing in you—a balance in your body." (I40)

"You have five drops [of the homeopathic remedy] in about an inch of water. I just followed the instructions, what came of it. […] Wait about ten minutes, but get up early and take the medication and go out with dog and then I know that time, is it says don't eat or drink or brush your teeth and things like that for at least ten minutes after taking it. […] There is no taste to it or anything like that now. It's just like having water in your mouth, that's all it is." (I14)

Some patients described *challenges with taking homeopathic remedies* or *procedures they experienced as strange*, as shown in one of the previous examples of a patient who was instructed to avoid coffee and mint. Another patient found it difficult not to touch the pills and anticipated how the small pills might be particularly *difficult to take* for some patients and the fact that the remedies were to be taken apart from meals might reduce patients' willingness to receive the treatment:

"Taking the remedy. It was difficult not to touch it, cause it's so small and round, it rolls everywhere. She sent five or six and I only needed one. The physical nature of the pill could be problematic. If it could be introduced into the pill, so you could pick it up with your fingers it might help, particularly for old people, and people who have difficulties with hands. […] "I take them late at night, that is fine, but I can't have anything to drink or eat before or after. You've got to know that you won't have anything from before to after the remedy, that is you have to plan. It's a conscious decision which in people's normal life may put them off from taking it." (I)

Summary of patients' experiences with taking homeopathic remedies

In summary, patients described the ***FORM AND AMOUNT OF HOMEOPATHIC REMEDIES***, as well as the ***PROCEDURES FOR TAKING HOMEOPATHIC REMEDIES***. Patients took either single or daily doses of homeopathic pills or daily doses of liquid remedies. Some *challenges* were described with taking homeopathic remedies. Other than this, little data was collected to describe patients' experiences of taking homeopathic remedies, other than what is reported under patients' experiences following homeopathic treatment and their understanding of how homeopathic treatment may work.

This brings us to the third section describing patients' experiences with treatment provided by homeopaths, describing how patients "made sense" of some of their experiences.

6.9.3 Knowledge, beliefs and understanding of homeopathy

Patients developed their knowledge, beliefs and understanding of homeopathy through their experiences with the consultation and with taking homeopathic remedies. Their knowledge, beliefs and understanding provide important information on how patients "made sense" of their experiences. Some of their thoughts derived from information received throughout the treatment period, from a variety of sources including their homeopaths, other patients, the media and the internet. Three themes have been developed for this section, ***ADAPTED TREATMENT***, ***CREDIBILITY*** and ***UNCERTAIN AND COMPLEX***

WORKING MECHANISMS. Results are also presented in table 35 (Qualitative interview study – Patients' knowledge, beliefs and understanding of homeopathy at 6 months).

Table 35. Qualitative interview study – Patients' knowledge, beliefs and understanding of homeopathy at 6 months

Themes*	Sub-themes*	Patients' descriptions
Knowledge, beliefs and understanding of homeopathy		
Adapted treatment	***Holistic and condition-specific*** ***Complementary and alternative***	Treatment tailored to patients and problems; homeopath prescribing to the individual patient; recommendations for lifestyle changes; addressing specific symptoms, disease or body part
Credibility	***Strengthened credibility*** ***Uncertain about credibility***	Produced in pharmacies; university degree; responses to criticism in the media; committed and professional; thorough; providing explanations; referring to research; competent; open-minded
Uncertain and complex working mechanisms	***Uncertainty*** ***Complex working mechanisms***	Uncertainty about working mechanisms; don't know how treatment works; providing suggestions for working mechanisms; uncertain about benefit of homeopathic remedies; Combination of factors – remedies and consultations; no doubts about benefit of consultations; "mind over matter" effect; external factors; other possibilities; doesn't matter as long as it works

* Themes and sub-themes developed on the basis of patients' descriptions at 6 month interviews

ADAPTED TREATMENT

The first theme, ***ADAPTED TREATMENT***, refers to patients' descriptions of how they perceived homeopaths *tailored* the treatment to patients and problems. This consists of two sub-themes, ***holistic and condition-specific*** *treatment*, and ***complementary and alternative*** *treatment*.

Patients described the treatment provided by the homeopath as being ***holistic or condition-specific***, and in some cases as both. One thing these descriptions had in common was a perception that the homeopaths were trying to *tailor* the treatment, providing them with ***ADAPTED TREATMENT***. The more ***holistic*** approach was understood as the homeopath prescribing a remedy for the particular patient, as opposed to prescribing it to fight a particular symptom or disease, or treating a body part. The ***holistic*** approach was seen as

one where the homeopath took many or all of the patient's symptoms into consideration, as described by the following patient:

> *"[It's] a treatment of the whole person, in mind and body. It's a more intimate knowledge of that person and that the treatments are tailored specifically for that person. That's how I see it." (I28)*

This ***holistic*** approach could also include the use of different approaches for one and the same patient, not only the prescription of homeopathic remedies, but also *recommendations for lifestyle changes*, as illustrated by one patient:

> *"[The homeopath is] looking at your whole being. It's not just a case of take this and it will do such and such. They are looking at your whole, the whole body, your whole person. Your physical, your mental, everything. It's just a different way of looking at people. […] If you have got an issue, of any sort, erm, then I think you should look. Lifestyle, diet, which is another issue. The homeopathic side and things that you are lacking and proper nutrition. General fitness and general health and everything, the whole makes up a whole." (I23)*

Other patients also explained what can be considered a ***holistic*** approach, but were less certain about their understanding, such as the following patient:

> *"To be honest, I don't really understand homeopathy. I didn't understand – she obviously tried to explain it at first. It is dealing with the, it's dealing with the physical symptoms, I think which help with your mental. If you are feeling better within yourself then you don't feel as bad as you used to feel. […] She literally goes through your whole body and says, have you had this and have you had that. And erm, then she will say, right, I know what that is and we will adjust that so it's like she adjusts the tablets to what's happening with your body, which is really weird." (I36)*

The second way in which patients understood the homeopath was tailoring the treatment was the ***condition-specific*** approach. This was described as a way of *addressing* some of the patient's *specific symptoms*, a particular *disease* or a *body part*. Nevertheless, patients

still understood this as being ***ADAPTED*** to each patient, as opposed to prescribing the same remedy for all patients suffering from the same problem.

> *"[The homeopath] put me on some medication for my knee, for the arthritis. She gave me some sea grass and I can remember that for the, I have asthma and she thought it could be hay fever as well, because when it's hot, I can't breathe properly. I've only took it when I've needed it." (I17).*

Some patients also understood the approach of addressing the current problems with particular homeopathic remedies as being holistic, as explained by the following patient:

> *"[She] tailors everything to whatever the current issue is. At first it was to treat the depression, then it moved onto fixing my headaches and now it's to do with my PMT. So it's kind of progressed as my health progressed. [Through] talking in interviews that I had with her regularly, she's identified that I have big problem with anger during PMT, so she's now sent something different to help regulate that. It's not treating my actual depression itself, but it's treating the other symptoms that go around. It's a very holistic kind of therapy." (I32)*

The same patient also illustrates the second sub-theme of the theme ***ADAPTED TREATMENT***, whether patients understood the treatment as ***complementary*** or ***alternative***. The ***complementary*** model was most commonly described by patients and was seen as *running in parallel* or *integrated with conventional or other treatment*:

> *"I kept everything that the doctor kept me the same and then obviously the medication from the doctor changed then I informed [the homeopath], cause it's got to be complementary, it's not instead of, and you can't just come off the Fluoxetine, straight like that anyway you need to taper it down." (I32)*

Some patients also described how different therapeutic approaches could contribute to a *cumulated effect*, as explained by this patient:

> *"It was at the same time I was having the CBT therapy. [The homeopath] tried to get it to go a bit hand in hand with what I was going through with the therapy. […] I*

would make a connection or something she would say and I would make a connection. I was then able to take that back to the [CBT] therapy appointments because it wasn't something that I had thought of and it wasn't part of the discussion I had had then. (I45)

Other patients were *uncertain* whether treatment provided by the homeopath would work together with conventional treatment, and the parallel use of both made it difficult for some patients to *determine causality of effect* of treatment:

"I don't exactly know how [Fluoxetine and the homeopathic medicine] work together. I don't really know how they work together as such. I know that I feel a tad more better, because obviously I'm still on the tablets and I haven't had a break or anything for quite a while and I have been having my past ones." (I40)

"I am on the Amitriptyline and I know that that does work with the pain relief. I don't know about the depression, but with the pain relief it does work. But yes, [the homeopath] has given these drops to see and it can't – it would be better maybe if I weren't on the Amitriptyline to see whether [homeopathy] has any sort of effect. […] I don't feel there has been a conflict only in whether that [the homeopath's] drops are working." (I28)

The second, and much less common, view was that homeopathy worked or could work as an ***alternative*** to conventional treatment, although such a line of reasoning could also be considered to be ***complementary*** or ***integrative*** in the sense that they could be used *consecutively* where homeopathy could be offered as an alternative option within a clinic where patients could then choose one treatment or the other, and in case of no success, move on to the other alternative:

"I think having something like [the homeopath] in the surgery, where you could actually vote to go see [the homeopath], against seeing a doctor. And I don't mean for something serious, I am talking about for this kind of guidance and help. I think it would be preferable for some people because drugs is not always the way to go because people are – some people are anti-drugs. […] I think it's a benefit and probably more cost effective than getting somebody hooked onto a drug they might

not be able to come off of. […] I think the national health should look into it and have it as part of the option because what is it, prevention is better than cure? They say that all the time, don't they? And having somebody talk, I know they say, we can pick up a phone and talk to Samaritans, but you don't always want that. That isn't what you're after. A quiet voice on the end – you just want somebody who will listen to you just rant. (Laughs) And be able to then maybe have something that they can do about it or help. [They] might have something that they can turn on and say well, would you like to try this, it's not the chemical drug. It's all natural and you'd be able to try it. And if you find it doesn't work, you know you can go and talk to a doctor because some do need a lot more help than just analysis type conversation but sometimes I think a good homeotherapist could determine something or refer." (I27)

CREDIBILITY

CREDIBILITY is the second theme developed from patients' descriptions of their knowledge, beliefs and understanding of homeopathy after 6 months of homeopathic treatment. Patients described thoughts, things they had heard or read and experiences they had with the treatment that either ***strengthened the credibility*** or caused them to feel ***uncertain about the credibility*** of the homeopath and the treatment.

Issues that made patients doubt or feel ***uncertain about the credibility*** of the treatment included the *dilute nature of homeopathic remedies*, the *small amounts of medicine* patients were given, *medication procedures* that were seen to be either imprecise or difficult to understand, and *criticism published in the media*. The same patients did however make remarks that ***strengthen the credibility*** of the practitioner and the treatment or they nevertheless remained *open-minded*, thereby contributing to the overall ***uncertainty*** instead of describing reduced credibility of the treatment. The following statements provide examples of these issues:

"[It's] minute amounts and whatever chemical she is putting in when I were having the drops and that she actually diluted as you go along. As a rational person, I find that odd that that happens. I am open-minded." (I28)

"I don't understand […] the therapies that she's using, how that can help. I've got five little tablets and I've taken two. They are just like little sweets. I just think, how, if I'm not seeing her for 4-6 weeks, how can those little five tablets help? I imagine that it's a mixture of all different things. I'm a bit sceptical, but not in a nasty way. I'm willing to give it a whirl. [If] it was proved to be effective then I think it would help a lot more people […]" (I10)

"I had to bang the bottle, tap the bottle five times and I shouldn't tap it four and I shouldn't tap it six, I should tap it five times. That was to agitate the contents. She explained very carefully how I should take them. That to me seemed a little bit like witchcraft. [I was told to] just take one gulp and then throw the rest away. As much as I want it to work, I just think again that seems a bit random and not very scientific, in a way. So that's made me doubt its efficacy. [It] does seem a little bit non-scientific, because it came through the post, but on the bottle it says to agitate it as little as possible. I thought, well, it's been in the post. It could have been all over, being shaken up. […] I came to the conclusion it's very scientific, because [the homeopath] once talked about the pharmacist. I think she talked about the remedies are made up at the pharmacy. [And] she's got a BSc, so it must be very scientific" (I2/I18, same patient)

As shown here, remarks that ***strengthened the credibility*** included the remedies being *produced in pharmacies*, the homeopath having a *university degree* and *responses to criticism in the media*. Additional remarks ***strengthening the credibility*** of the treatment included homeopaths being perceived as *committed* and *professional*, doing a *thorough* interview of the patient, as well as providing *explanations* as to how the remedies may work and *referring to research*. The homeopath being *committed* and perceived as *competent* and *thorough* has already been presented as sub-themes that came out of the patients' experiences with the consultations. We now see how this contributed ***strengthening the credibility*** of the treatment, as illustrated by the following examples:

"Aside from professionalism or obvious passion about what she does [she's] got an aura about her and she's a special lady in the right role. […] She's a colourful character but very, very committed to what she is doing and that gives you a lot of

confidence. Sometimes, that's all the placebo that you need when you're talking about mental health." (I21)

"She explained about how it's the sort it – what do they call it, is it like the memory of it that's in the carrier." (I12)

"It feels quite scientific and quite, the questions are quite short. She quite often will ask me to expand on something which then obviously makes me think in a way that perhaps I hadn't previously thought. […] I feel she's looking for more precise answers [And] perhaps it does feel perhaps more scientific even though, as you know I am not a convert to homeopathy. I realise that she's, there is an awful lot of research behind what she does." (I19)

UNCERTAIN AND COMPLEX WORKING MECHANISMS

Data was also collected in order to understand patients' views on how the treatment may work, and if they thought it worked. Almost all patients commented on working mechanisms, either on their own initiative or when asked specifically about it. Patients' responses resulted in development of the theme ***UNCERTAIN AND COMPLEX WORKING MECHANISMS***. ***Uncertainty*** *about working mechanisms* was expressed by many patients stating they *do not know how the treatment* works, as shown by this example:

"I haven't got a clue. I really don't know what they are actually doing or what it is achieving with me taking them […]" (I42)

Most patients who expressed ***uncertainty about working mechanisms*** nevertheless *provided suggestions* as to what may have caused the changes in their mood or state of health. Many patients who were uncertain about how treatment worked, as well as those who seemed to be more clear or convinced about their ideas, presented somewhat ***complex working mechanisms***. They were of the understanding that changes in their state of health had resulted from a *combination of factors*, most commonly referring to the effect of the *homeopathic remedies* and the *consultations with the homeopaths*, as illustrated by the following examples:

"It's not just the medication, it's the whole session that helps. […] I don't think it's just the remedy part of it. I think it's the whole package. It's good the three quarters of an hour I see [the homeopath] that helps me as well as so I am thinking well, if that's helping me maybe the remedy itself will help me as well. […] It helps you in more ways than one. If the remedy side of it doesn't turn out to work as well as what I would hope, I'm still benefiting by the other part of it as well. I am hoping the remedy part will help as well. It's not the be all and end all, because I think the package itself helps." (I31)

"It wasn't just with [the homeopath], the help wasn't just remedy. I was able to talk about things as well and she was also able to offer a bit of advice, erm, with other things, so that the two are very much hand in hand." (I45)

None of the patients interviewed expressed any doubts about the *benefit of consultations with the homeopaths*, but some were *uncertain* as to *whether the homeopathic remedies helped* them or whether their improvements were the results of a *"mind over matter" effect*, as suggested by these patients:

"The medicine what [the homeopath] gave me, I felt I were feeling better with it and when I'd been to see her and when you can speak to somebody about your problems, well not problems, being depressed and things. I said to [the homeopath], last time, that I were feeling a lot better, yes. […] I felt better these last few months than I have done in a very long time. Whether that's due to the homeopathic medication, I don't know." (I17)

"[She] changed the medication and I have more improvement, a big improvement since she's changed to the latest one, which I believe is called Sepia. I think also it helps to talk to people about problems and stress and things like that. I think it's a combination of talking to someone helps as well. […] I get anxiety attacks. They calm down instantly that I started on the Sepia, the panic attacks went a lot less. And talking to her obviously helped a lot. […] It could be mind over matter. It could be that you think, I am taking this tablet therefore it's going to make me feel better." (I39)

Although many patients seemed to believe that the *consultations with the homeopath* and the *homeopathic remedies* could explain why they felt better, some acknowledged the *effect of external factors*, as explained by the following patient:

> *"The first time everything seemed to be fine, but as soon as I came off [the homeopathic remedy] I relapsed. When I was put back on them again it was okay towards the end when I relapsed, but that was because I had a really bad time at the time. And then again, I had an appointment just before my friend died and of course when he died that really got to me. […] It may only be psychological. I don't know. I don't think it is, because like I said, when I was taking it it seemed to work when I stopped taking it didn't work and even when I was taking it, I still had the odd relapse even though I was taking it. Maybe not as frequent or as heavy, but I still had the relapses. It all depends on the amount of stress I am going through." (I24)*

Some were more *uncertain* whether they had felt an improvement as a result of the treatment or whether this was due to *factors outside the treatment* such as changes in life circumstances.

> *"During the later spring I would say that it did decrease, but it's hard to say whether it's because of the treatment she were giving me or because of the nature what I would be doing at work. […] It could have been just because I were talking, I were talking a lot but maybe nothing to do with the drops. I don't know. I can't say for certain. I got overall better in myself and had a more positive attitude to my life and so on than I did before. When I first saw [the homeopath] I were really down in February. I did feel better once I started." (I28)*

Some pointed out that they were *not so concerned* with how treatment works, *as long as it does work*, as seen in the following statement:

> *"It almost doesn't matter. The fact is if you feel better then things are better in your life, you know if you feel better." (I29)*

In addition to the explanations already presented, a whole range of possible explanations for improvements in patients' state of health were suggested, such as the effect of *self-*

reflection, becoming more *balanced*, the *"knock on effect"* on depression through reduction of pain, and explanations such as *"it works on what is wrong"* or referring to the *"principle of similars"*. Overall, these explanations contribute to the sub-theme ***complex working mechanisms***.

Summary of patients' knowledge, beliefs and understanding of homeopathy

In summary, three themes were developed on the basis of patients' descriptions of their knowledge, beliefs and understanding of homeopathy, after having received homeopathic treatment for roughly 6 months. The three themes were ***ADAPTED TREATMENT***, ***CREDIBILITY*** and ***UNCERTAIN AND COMPLEX WORKING MECHANISMS***. Patients understood treatment as *adapted* either to their condition or to them as a whole. They mainly considered the treatment provided by a homeopath as *complementary*, as *running in parallel* with conventional treatment. Some of their experiences, what they had heard and read contributed to strengthening the ***CREDIBILITY*** of the treatment, whereas other elements made them feel more ***uncertain*** about it. Many patients felt ***uncertain*** as to *how the treatment works*, but nevertheless had *suggestions* for what might have contributed to any improvements in their mood and overall health. Understanding of possible explanations for improvements included a variety of factors, most commonly the consultation with a homeopath and the homeopathic remedies, although patients acknowledged the complexity of understanding causative factors and some expressed uncertainty as to whether their improvements were caused by *factors outside treatment* in everyday life.

6.9.4 Changes in knowledge and understanding from before to after treatment

Patients' knowledge and understanding changed considerably from the first interviews that took place 1-2 months after patients started treatment to the interviews that took place after 6 months. They went from having ***no knowledge*** or having some ***assumptions*** which were more or less accurate, to describing it as ***ADAPTED TREATMENT***, which was either considered to be more ***holistic*** or ***condition-specific***, and most commonly ***complementary***, running in parallel with their ongoing conventional treatment. Very few patients suggested any such ideas at the onset of treatment. There was still considerable ***UNCERTAINTY*** about the working mechanisms, but many patients seemed to describe what can be understood as ***COMPLEX WORKING MECHANISMS***. They acknowledged the benefit of consultations and

many also described a combined effect between the homeopathic remedies and the consultations. Thoughts about the ***CREDIBILITY*** of the intervention were much more pronounced at 6 months, with patients presenting many more issues that either ***strengthened the credibility*** of the treatment or that contributed to patients' ***uncertainty about the credibility*** of the intervention.

6.9.5 Changes and lack of changes in patients' state of health

This section describes patients' descriptions of changes in their state of health, or the lack of such changes. Seven themes have been developed to describe patients' experiences (table 34: Qualitative interview study – Patients' experiences with treatment provided by homeopaths):

- ***IMPROVED MOOD***
- ***IMPROVED WELLBEING AND ENERGY***
- ***FEELING MORE BALANCED***
- ***IMPROVED COPING***
- ***PHYSICAL IMPROVEMENT***
- ***LITTLE OR NO CHANGE***
- ***ADVERSE EVENTS OR FEELING WORSE***

The most commonly described change following 6 months of treatment was some form of ***IMPROVED MOOD***. Patients described improvements in mood in various ways, most commonly *feeling less depressed, less anxious* and having *fewer panic attacks, feeling less irritable and less short-tempered.* The reduced feeling of being depressed is illustrated by the following patient's statement:

> *"I didn't find any change [after the first homeopathic remedy]. And then when she put me on the other ones, she put me on the added one on a Friday and I did find that I was on a level. I wasn't experiencing either highs or lows. I was just quite normal. [There] are times when I do feel depressed. I must say that since I've been on these tablets, I haven't had any depressions downs or ups. I have just been quite normal. [The antidepressants] seem to keep me on a level. But erm, I do think—I've been on*

them a long time, the same ones. Erm, but I must admit that with the ones that [the homeopath] has given me erm, I feel even more calm. It is nice to talk to people, to talk to [the homeopath]. I feel much happier in myself. […] I am not going down into the depths and being miserable, very miserable. Erm, more on a level with myself. I am happy in myself." (I25)

Table 34. Qualitative interview study – Patients' experiences with treatment provided by homeopaths (continued)

Changes and lack of changes in patients' state of health		
Improved mood		Less depressed; happier; dark cloud lifted, stopped self-reproach; less anxious & panic attacks; less irritable/short-tempered; temporary/sustained improvement; life circumstances contribute
Improved wellbeing and energy		Feeling better in general or overall; improvement of several symptoms; increase in energy
Feeling more balanced		Reduced anxiety; calmer; more relaxed; less irritable or aggressive; sleeping better; but will always be a bit "hyper" or "fiery"
Improved coping		Handling work; ability to cope/manage life; reduced isolation and self-harm; increased socialising and self-care; coping with past/current emotions; letting go of the past; living in the moment; seeking additional answers and help
Physical improvement		Reduced: chronic pain; headache; vertigo/dizziness with nausea; cramps; menstrual periods; breathing problems; heaviness in feet; eczema, cuts and bruises; reduced conventional drugs
Little or no change		No or short-lasting improvement; slight/temporary improvement; relapse after consultation
Adverse events or feeling worse		Variety of transient symptoms, mostly mild, some moderate or severe; headache; pain in chest, jaw, neck and back; slight vertigo; uncertainty about causative link; no diagnosed disease; homeopath reassured patients; homeopaths aware

* Themes and sub-themes developed on the basis of patients' descriptions at 6 month interviews, experiences with the consultations and homeopathic remedies also from 1-2 month interviews

The following patient, who was also taking antidepressants, described feeling *improvement in depression*, *feeling happier* and *stopping self-reproach* for things going wrong. There seemed to be a more *sustaining improvement*, whereas in the past the *feeling of depression* would still come every now and then, in spite of taking antidepressants:

"I've always had depression. Sometimes it flares up worse than what it is. I've been fine this last few months […] I feel happier in myself. I am not depressed and I don't feel sad. […] I feel happier and I don't pull myself down. If things go wrong I used to blame myself. It must be my fault and, I am all right. […] The medicine what [the

homeopath] gave me, I felt I were feeling better with it and when I'd been to see [the homeopath] and when you can speak to somebody about your problems, well not problems, being depressed and things. I said to [the homeopath], last time that I were feeling a lot better, yes. […] I think it's worked. It's made me feel happier in myself. […] Even though when I was taking antidepressants, which I still am, some days I would feel really down. Just lately I've just been feeling fine all the time." (I17)

Some patients did not use the word *depression*, but described it in other ways such as a *dark cloud that lifted* as they felt better, indicating ***IMPROVED MOOD*** and *reduced feeling of depression*:

"I would say within 48 hours of taking it [...] I've got this grey cloud above my head. Then it kind of went to blue as if it had lifted a bit. […] because I could feel this thing in my body and making me feel lighter or like I said this grey thingy blue." (I26)

Other patients described ***IMPROVED MOOD*** as ***improved anxiety***, ***reduced panic attacks***, ***feeling less irritable*** or ***less short-tempered***, *and less sensitive* to seeing or hearing bad news, as illustrated by the following patient statements, with some patients feeling more considerable improvement and others with less obvious and only temporary improvements:

"I used to suffer really bad with anxiety and things like that and I never suffered—I am not saying that the tablets had done this, but I have never suffered with any bouts of anxiety since I have been taking any of these tablets what [the homeopath] has given me." (I38)

"I don't think they're doing very much. I don't think I am quite as quick tempered as I have been, because with being in pain all the time you get very, very quick tempered and you get fed up. I snap quite a bit. My wife's noticed that I am not quite as snappy as I were before. So whether that has got ought to do with homeopathic medicine, I don't know." (I43)

Other patients also explained how *life circumstances* could contribute to the return of symptoms. In the following example the patient experienced improvement of depression,

but relapsed following the loss of a family member. (Note: LC30s in the following quote refers to a particular homeopathic remedy):

> *"I was actually getting okay. [The homeopath] who I saw gave me some LC30s I think they were that really bucked me up and I was coming along fine and then I had a family bereavement. [Up] to six weeks ago, seven or eight week ago, I was doing fine. I was coming out of my shell, the black dog as I call it, depression. I call it, the black dog. Erm, I seem to be getting better with the help of the tablets that she's given me. […] When [the homeopath] gave me them I felt champion, really good. The best I have felt for years to be honest. [And] then I lost my [family member] and that like. […] I was coming out of myself and the depression was going quite quickly, you know. I thought, lovely, I am for once I am getting out of this situation whereas I am not full of tears all the time and what have you. Silly little things, like the children in Africa with the Ebola and things like that, that really upsets me. You know what I mean? This time I haven't been as upset over it or I wasn't, you know. Yes, I were doing okay. […] I was having a panic attack again like and I couldn't breathe. […] That got better. That actually got better, but since I've lost my [family member] and that, I have started with panic attacks again. […] I could feel the change. I felt a lot happier. My son commented at the time and he said, what's up with you, have you got a new bird or summat like that. I said, it's tablets, it must be. He said, good, it's doing you good like. […] He said, you are not a grumpy old bastard any more. […] It just seemed like you know the magic bullet as they say, that's what it seemed like, the magic bullet. It were more or less instant, within three days, that's good going." (I35)*

However, for some patients the improvement seemed only to be *temporary* and only took place and lasted shortly after the consultations with the homeopath, as described in the following example:

> *"I did start to feel a little better and I was lot more positive about we were thinking about moving – you know future, which I haven't really done because I've been so stuck in grief. [The homeopath] did give me another remedy. So loss type remedy after that. […] Not really [improved then]. I suppose I only had that maybe only a couple of weeks. But I sort of, I've been feeling okay, like – I feel better than I expected to feel. [Whenever] I go to see [the homeopath], I come out feeling quite*

buoyant and kind of positive about life and quite happy […] I wonder very much if that's going to [the homeopath] and maybe if I saw another practitioner or maybe I wouldn't like them so much and it only be get as much from them or get on with them." (I29)

Several patients reported feeling ***IMPROVED WELLBEING AND ENERGY***. This included descriptions of *feeling better in general or overall*, as well as description of *improvement of several symptoms* which added up to the overall feeling of ***IMPROVED WELLBEING***, as explained by the following patient:

"[The homeopath] prescribed some Sepia. So I tried those. And within a few days I could feel the difference. I was totally amazed, I felt calmer, I began to start sleeping better, the cramps finished and I generally was feeling a little bit better. […] It was a case of sense of feeling wellbeing I don't know, yes, and as if I am getting in tune with my body […] I don't know, just have the general feeling of wellbeing, I don't know, but that's what I felt as if it did not just made me feel better in one way, better in multiple ways, you know like I didn't get the night cramps. I was able to dream. I felt more relaxed. And you know, just this feeling of feeling well. Just kind of if you feel body had a good reaction to things. Tiny little things. […] My whole body was feeling better from it. It's just not, just one bit. The whole thing." (I26)

Some of the patients described having suffered from lack of energy as part of their depression, and following treatment an *increase in energy*, as explained by the following patient:

"I did feel, I felt better. I felt no more lead in my feet. I felt I could breathe again. I could take a deep breath whereas before I saw her, I was taking like shallow breaths and I was feeling that oppression again. Before I saw [the homeopath] and after the remedy it was an amazing month. I really did feel great. […] I was in a massively depressed state. I had incredible lethargy. [My] feet felt like I had lead in my feet. I could hardly do anything. I couldn't do any housework or anything. […] I honestly believe [the homeopathic] remedy made an immense difference to me that month. It lasted a whole 30 days that one remedy." (I44)

Several patients described what has been understood as ***FEELING MORE BALANCED***. They could feel *reduced anxiety*, feeling *calmer*, more *relaxed, less irritable or aggressive*, and for some it resulted in being able to *sleep better*, as illustrated by the following patient:

> *"I didn't feel anxiety and if I did it was easier to manage the feeling that I needed to escape when I felt anxiety filled I always felt like I had to, I needed to run away from whatever was causing my anxiety. And I used to feel a lot more panicking but now I don't feel that any more of panicky and at night as I used to. I feel a lot more calmer in myself. […] My partner thinks I am more chilled and more calmer in the evenings and managing a lot better. I am not as erm, how did he put it? You don't tend to be climbing the walls late at night. You tend to be sleeping a bit more. Tend to be more restful than I used to be and that's what he says. […] He says you don't seem to be – you seem to be going to sleep. You might sleep for four or five hours now whereas it was sleep, wake up, sleep, wake up. You wake up by every hour. And he said, now you sleep fully and you don't seem as distressed, he said." (I41)*

As described by this patient, some described how people around them also had noticed their changes. Although several patients did feel more *relaxed* or used other terms to describe how they were ***FEELING MORE BALANCED***, some realised that they had personality traits that would probably always make them to be a bit more *"hyper"* or *"fiery"*, as illustrated by the following patient statement:

> *"[The] tablet did or the therapy did bring me to a point where I was like more chilled. Definitely more relaxed. Not as hyper over things, not as aggressive over things. […] I think over the period of time when taking them I've got to a very nice plateau of being quite chilled. I'll never be, you know laid back and relaxed, and we're always going to have that fire desire issue and there is ginger hair and other factors that will cause me to have a fire but it was definitely an improvement on my moods and improvement on the swings as well […] as time did go on, my husband did say, you're calmer. You're not as aggressive, and you're not as augmentative and things like that […]" (I27)*

Several patients described improvements in their mood which also helped them with ***IMPROVED COPING***. This could be described as slight *improvements in handling work* such as described by one patient:

> *"I seem to be handling work a little bit better in the fact that I am recognising that I can only do so much. Erm, I just have to kind of to deal with that that you know, I can't work any harder and I can't work any faster and therefore I just have to kind of do what I can do and I have to leave it and I think I am coping better with that. […] The fact that I do kind of used to bring it home all time and want to do it at weekends and I just think I can't possibly fit any more into my life with home erm, and with work. I think I have come to terms with that. So whether that's a benefit of seeing [the homeopath] and the remedies, I could put it down to that or the fact that I am talking to somebody independently about it sort of thing probably helps." (I34)*

Other changes could be more significant, such as *improved ability to cope* or *managing life* in the following example, where the patient's changes resulted in *reduced isolation*, *increased degree of socialising, reduced self-harming* and *improved self-care*:

> *"I have been a lot more positive and I've been getting up and going out. Something I haven't done in a long time. […] I went for a walk up the lake. I haven't done that in over two years. It is having a positive effect on me. […] I have never opened curtains in two years in my [home]. In the last week or so, I've had my curtains open two or three times during the week. I'm going out a lot more rather than isolating myself in my [home]. I am socialising with people rather than keeping away from people. […] I was either self-harming or I had my headphones stuck in my ears, my MP3 player at full blast for seven days straight. It was just my way of coping with things. I haven't done that recently. I feel a lot happier […] I'm optimistic. […] I'm actually getting round to cooking something […] I came and saw [the homeopath] still feeling fine. I was still high. I was still happy. I was enjoying myself. And she didn't prescribe me anymore, because it seemed to have helped. And then I just went downhill again. And then I came to see her again, I'd hurt myself and this and that and the other and she ended up prescribing it again. [The homeopath] still gave me another dose to try and keep it working as I was on it. It seemed to keep me okay." (I15 & I24)*

Other patients improved their ability to *cope with past and current emotions*, a sense of *letting go of the past* and *living in the moment* as shown in the following example:

> *"I think I had learned to let go of the past a lot and try and stick with, and she tried to bring me into the here and now and bury the past, kind of. Things that had troubled me I have been able to let go of, finally after a long long time. I feel like it's all gone. I am not thinking about any of that any more. That is amazing. Things I have carried around with me for 20 odd years that I get really upset about and just gone now, which is a big turnaround. She tried to get you to live for each day, I think and make you think a bit more about living in the moment. […] This is now when you are living in this moment and what were be to happen if you found out you were terminally ill or something? You would want to live every moment and see every tree and listen to every bird and listen to nature and things like that that we take for granted. Makes you think a bit more rather than worrying about everything. […] We talked things through and look at it from different ways and then just close the door and then think, I am not going to spend any more of my life thinking about this and don't want to talk about it again. It's done, gone. I've never been able to feel like that. Now I can get on with my life." (I39)*

The same patient also explained how the process she had been through as part of the treatment she had received contributed to her *seeking additional answers and help*:

> *"It's made me go and research things and buy books on positive thinking and living in the moment and things like that made me look into self-help books and relaxation and meditation and I have started doing yoga trying to calm it all down. I'd rather do things to help myself that are natural than, I once went to the doctors and I was horrendously stressed and they just prescribed me some tablets and when I read the side effects on them I refused to take them." (I39)*

Some patients described ***PHYSICAL IMPROVEMENT***, in particular *reduced chronic pain* and *improvement in headaches*, and more rarely also *improved vertigo or dizziness with nausea*, *cramps*, *menstrual periods*, reduced feeling of *breathing problems*, *heaviness in*

feet, temporary improvement in *eczema*, and help for problems with *cuts and bruises*. Examples of patients' statements include:

> *"I was getting really bad headaches. I think they was stress headaches that I was getting and then I were having nightmares. [The homeopath] gave me some tablets to take and over a period of time the headaches got better. It wasn't as erm, they wasn't as painful as what they was at the beginning. Obviously, I don't know if it's a change of circumstances or the tablets, but it might have been a combination. […] I'd been off work with maternity leave and then I had had a little bit of sickness. I had been on the tablets that [the homeopath] gave me and then she gave me some more tablets because I had a lot of pain in my hip and my lower back with sitting for long periods of time and driving for long periods of time. I was taking two different sorts of medication. That helped me sleep better. Obviously, I was tired anyway, but I thought that they was helping me sleep better because the pain wasn't as bad." (I38)*

> *"[I] stopped having headaches. I still have the odd few but they are not as frequent as they were. I can go all day without them. Now I only get them when I am really tired." (I32)*

Reduced chronic pain was also contributed to *reduced use of conventional drugs* as described by one patient:

> *"It still aches a little bit, but the pain is not as severe as it was since I've been taking those. [The homeopath] gave me some tablets. I still am taking painkillers. It's, I wouldn't say it was better, but I can tolerate it a lot better. The pain doesn't seem as bad. […] I am taking them four times a day and perhaps I am only taking them twice now. As I say, the pain is still there, but not as severe as it was. I am tolerating it. Whether it's mind over matter, I don't know. […] I used to wake up in the night with pain and have to take tablets. I haven't." (I17)*

Although most patients described improvements in their mood and other forms of improvement in their health, some experienced ***LITTLE OR NO CHANGE***. This was in some patients described as *no improvement* at all, in others only *slight or temporary improvement*. Patients did not express any dissatisfaction with their homeopaths, but were

happy with the consultation and viewed these as has been described in the section on experiences with the homeopathic consultation. In the following example, the patient also conveys the homeopath's hopes for the treatment:

> *"She has tried three, maybe four remedies on me. I don't think either of us feel that we are having much success, really. […] I feel bloody miserable and don't want to do anything except sit here feeling bloody miserable. […] I still wouldn't say absolutely it's a load of rubbish. Neither would I say, it's fantastic and it's worked for me. […] When we first started she said that she hoped that at the end of the process I would feel more upbeat and more like going off and exploring or just feel generally more cheerful and that I would probably be sleeping better. I have also got eczema and she said, that would probably get better. Nothing has happened, really." (I19)*

The satisfaction with the consultation with the homeopath is also illustrated in the following example, where the patient describes feeling sl*ightly better during the consultation*, but feeling just the *same again shortly after*, when returning to his everyday reality with a dying family member:

> *"[My depression is] just the same I think. [My anxiety is] more or less the same, apart from the fact that the reality of her life coming to an end is more prevalent now. I feel a little bit at ease as if I've been talking to someone about my problems, just makes me feel a little bit better. [It lasts] not long afterwards, but it just makes me feel better at the time. Once I've got back to my daily life and its back to normal." (I42)*

Some patients experienced slightly longer, but still only a *short-lasting improvement*. In the following example, the patient had been prescribed four different homeopathic remedies with no effect, but upon taking the fifth remedy, felt an improvement in her eating habits and her sleep. This effect only lasted for a maximum of two weeks, with no improvement following another dose of the homeopathic remedy. The patient describes her excitement when experiencing an improvement and trying to reason why it might not have worked.

"I don't think it's worked for me. I had about four sessions with [the homeopath] and it didn't do anything for me. I didn't feel any change at all. Then I think it was about the fifth [homeopathic remedy] where it seemed to work. [I] have problems with eating, overeating, bulimia and depression. So, erm, I didn't overeat with this particular tablet. I felt a lot better. […] I took this tablet on Sunday night and from the Monday without realising it, I didn't consciously do anything, but without realising it, I sort of didn't have any chocolate that day. I didn't have a craving for it, which was weird because I normally do eat a lot of chocolate, like I say. I didn't have a craving for it and then the next day I went to gym and I felt really good and I was eating a lot more fruit and I never cook a proper meal. […] After a week and a half I was actually having meals at night. It was really good. I felt so much more vibrant and positive and happy and yes, I just felt really good and then […] it just seemed to stop and so I took another tablet and she said that didn't seem to work as well. […] I was very excited when it started to work, because I've had lots of treatments for various things and none of them seemed to have worked and I was very excited when that one worked, but then I have gone back again […] I am not sure whether my body just doesn't take to a lot of tablets […]" (I36)

Although most patients reported improvements in their mood and state of health, several also described ***ADVERSE EVENTS OR FEELING WORSE***. Adverse events were presented in section 5.9.1 (Reports of adverse events following treatment by homeopaths). Some of the ***ADVERSE EVENTS*** were reported by patients during qualitative interviews and are also presented in table 19 (Adverse events in patients treated by homeopaths during the trial) and in further detail here.

A *variety of symptoms* were described by the patients who reported ***ADVERSE EVENTS***. The most commonly reported adverse event was *headache*, described as severe by one patient and occurring shortly after taking the homeopathic remedy. The same patient also reported *pain in the chest, jaw, neck and back* occurring a few days after starting the remedy and lasting up until the next day. Reported adverse events were *not diagnosed as diseases* by patients' GPs or specialists, as seen in this example:

"I felt very, very poorly one night. I had chest pains and erm, I had pain in my back and pain in my jaw and pain in my neck. I went to the hospital and they did a battery

of tests and said there was nothing wrong. […] I got the chest pain within probably four days of starting taking it. […] I suddenly got erm, an excruciating headache. I don't suffer with headaches at all, I'm very lucky in that respect. But it was so painful that I ended up in hospital […] At that point, I thought, I better stop taking it. […] I just wondered whether I'd got a blood clot or an aneurism or I just panicked, really. I just wondered if it could have been related to what I was taking. […] When I got chest pains I thought that was part of the course really that it could just be anxiety. But then when it went into my back, I worried, because that was something different, something that I'd never had before. […] The chest pains and the back pain were gone the next day. The headache had gone before I'd even got to the hospital […] [The homeopath] said, just dilute it a little bit more. […] I did worry. But anyway, she said, she reassured me." (I2/I18, same patient)

The *homeopath reassured the patient* that the treatment was not harmful, as also seen in another patient, who described *slight headache* together with *slight vertigo* occurring repeatedly and shortly after taking the remedy prescribed by the homeopath. This and some other patients expressed some *uncertainty about a causative link* between the symptoms and the homeopathic remedy:

"[The homeopath] told me that there wouldn't be any side effects. [Half] an hour after I've taken them, sometimes I've had just a little niggly pain in my head or just felt a bit dizzy. [It lasts] only a minute or two. It's not a big pain. It's just something that comes on as if somebody stuck a needle in your head and you've just got that little bit of pain for a minute or two. […] But again, that might not be relevant to the tablets." (I13)

Whereas a limited number of adverse events were considered by the researchers (PV and PF) to be *moderate or severe*, as described in the first example, most were considered to be *mild*. As described in the two presented examples, the *homeopath reassured the patient* that the treatment was safe. However, in another example the homeopath *reduced the dose* of the homeopathic remedy, suggesting the *practitioner's awareness of the potential for homeopathic remedies to cause adverse events* in patients:

"At first, the dosage was too high. She reduced it down. I can't remember now what the side effect was, but I definitely, that was the only thing. Headaches I think it was." (I23)

Adverse events were *transient*, described as lasting shortly, a few minutes or hours. A few were however described as lasting last for a few days, as seen in the following example. This example also illustrates how homeopaths could consider the adverse event to be linked to the treatment, although patients could express doubt:

"I started getting these mood swings. Getting irritable and which I am not, I am not an irritable person. It only lasted a few days. I told her when I saw her and she says, it must have been a reaction to medication and it were all right then and it must have settled down. I was thinking to myself, if you can make an adverse reaction then probably also can have opposite, a good reaction. […] I were in a sharp decline anyway. I think if it had been the elixir, I don't think it would have made a right lot of difference. I were really getting worse." (I31)

A few patients described what homeopaths refer to as a *"homeopathic aggravation"*, described in section 5.9.1 (Reports of adverse events following treatment by homeopaths). Such a reaction is considered to be a part of the "healing process" and is followed by an improvement in the patient's symptoms, as described by the following patient:

"As soon as I took the first remedy I noticed some effects. Ehm, one of them was, the first effect was an intensification of my fears. [And] I'd get a, a pressure around my forehead just here (pointing just above the root of the nose). Ehm, and I'd always have it throughout the day. And when I take the remedy that becomes very strong. […] Then what happen is it will ease off and recede more and more and that steadily has receded to a point where I can, I almost can't feel it. [So] even though my symptoms were intensifying, I would feel good. Ehm, it's a bizarre mixture of feeling […] more anxious, sweating more, which normally I would feel was bad, but in that situation it felt good, cause I, I would feel relief. Ehm, everything would become easier, making decisions, going out, on my own, would be easier. […] I'd had that experience of taking the remedy, each time, I'd go through an intensification and then I'd come out at like a better level." (I46)

Less commonly patients described a *decline in the state of health*, without this being considered to be an adverse event which was likely to have resulted from the homeopathic treatment. The following patient did also in the interview describe being less quick tempered (as described under ***IMPROVED MOOD***), but overall considered his health to deteriorate:

> *"[My] health is getting worse. I'm getting a lot more pain than I had before. Just generally not sleeping and not eating properly and things. You know what I mean? If it weren't for pain in my back my health would be pretty good. It's just all pain I am getting. […] I've got some damaged discs in bottom of my back. […] It has gotten gradually worse. It was going to get worse anyway." (I43)*

Summary of changes and lack of changes in patients' health

In summary, seven themes were developed based on patients' descriptions of their experiences following treatment provided by homeopaths: ***IMPROVED MOOD, IMPROVED WELLBEING AND ENERGY, FEELING MORE BALANCED, IMPROVED COPING, PHYSICAL IMPROVEMENT, LITTLE OR NO CHANGE,*** and ***ADVERSE EVENTS OR FEELING WORSE***. Most commonly patients described a feeling of ***IMPROVED MOOD***. Some would simply express it as ***IMPROVED MOOD***, whereas others described ***feeling less depressed*** using a variety of terms such as *feeling happier*, *a dark cloud that lifted* and *feeling more optimistic and positive*. Others referred to other aspects of emotional improvements, such as ***feeling less anxious, less irritable*** or ***short-tempered***. For some patients improvements were only *temporary*, whereas others felt more *sustaining improvement* in their symptoms, with or without the parallel use of antidepressants. Relapse of symptoms were by some patients described as resulting from increased levels of stress or bereavement.

The feeling of ***IMPROVED WELLBEING AND ENERGY*** was described as *feeling better in general or overall*, experiencing an *improvement of several symptoms* and *increase of energy*. Patients commonly experienced what was interpreted as ***FEELING MORE BALANCED***, described by patients using terms such as feeling *calmer*, more *relaxed*, *less*

irritable or aggressive, although some patients realised that some of their traits such as being "hyper" were linked to their personality and unlikely to disappear entirely.

Improvements in patients' mood and state of health did for many patients also contribute to ***IMPROVED COPING***. This could involve *improved ways of comping with or handling work or other everyday life situations*, and engaging in more positive behaviour such as *increased degree of socialising* as well as *reduced tendency to self-harm* and *improved self-care*. Some patients would also describe how they were actively *seeking additional answers and help*.

PHYSICAL IMPROVEMENT was reported by some patients, and the nature of such improvement *varied considerably* from patient to patient, illustrated by examples such as *reduced chronic pain, improvement in vertigo, menstrual periods* and *breathing problems*. For some patients, these improvements also resulted in *reduction in use of conventional drugs*.

Other patients described ***LITTLE OR NO CHANGE*** in their mood and overall state of health, with either *no improvement* at all, or *slight or temporary improvement*. Others reported ***ADVERSE EVENTS OR FEELING WORSE***. ***ADVERSE EVENTS*** included a wide *variety of symptoms,* most commonly *headaches*. Although symptoms were mostly *mild*, some were considered to be *moderate* or *severe*, but they were *not diagnosed as diseases* by patients' GPs or specialists. Although homeopaths in some cases *reassured the patients* about the safety of the treatment, other examples suggested they were aware that *homeopathic remedies could contribute to* ***ADVERSE EVENTS***. Adverse events were *transient*, mostly lasting for a very short period of time, but in some cases up to a few days. Some patients experienced a *decline in their state of health*, although they considered this as taking place in spite of, rather than because of, homeopathic treatment.

6.10 The trustworthiness of the results of the qualitative study

The trustworthiness of the results of the qualitative study depends on the credibility, the dependability, the confirmability and the transferability of the results, as pointed out in section 4.2.6 (Trustworthiness of the results from the qualitative interview study).

As described in section 6.1 (Selection and recruitment of patients for qualitative interviews), a purposive selection of patients was made with the intention to interview a variety of patients who had experiences with treatment by homeopaths, in order to increase the likelihood that they would represent a wide range of experiences with the intervention. The 33 patients included in the qualitative study represented both genders, different age groups, different socio-economic groups, and they lived in different parts of South Yorkshire. Patients with moderate, moderately severe and severe self-reported depression (measured using PHQ-9) were included. Interviewed patients were comparable to other patients in the trial with regards to all these characteristics, and also with regards to the number of long-standing conditions and BMI scores. They had been treated by different homeopaths providing the intervention. Patients were interviewed shortly (1-2 months) after having had their first consultation with a homeopath and after about 6 months in order to capture both their immediate and longer-term experiences with the intervention.

The use of audio-recording and transcription of interviews contribute to the credibility (and thereby trustworthiness) of the results, as would be common in most forms of qualitative research. Another person, who is a professional transcriber and who is not otherwise involved in the research project, carried out transcriptions, and these were checked by one researcher (PV) and in case of discrepancies in the understanding of interviews, by one or two other researchers. Agreement was reached on the understanding of all 46 interviews. This process thereby contributed to the accuracy of interview transcripts.

Interviews were planned to be carried out until saturation, when no new issues came up in additional interviews. The term "saturation" is open to interpretation and I made the decisions on when to stop the first round of interviews. It could be argued that other researchers could have identified additional issues. I did however carry out three consecutive interviews without identifying new topics and it therefore seemed reasonable to terminate the first round of interviews. In the second round of interviews, the set maximum of 30 interviews was carried out, adding up to a total of 46 interviews with almost half of all patients who received treatment by homeopaths in the trial. In order to allow patients to describe their experiences in detail, interview length was flexible and interviews did last for up to 119 minutes. Patients had been informed beforehand (in

writing and verbally) that interviews were confidential, meaning that their identity could not be revealed in the final published report.

I decided to not inform patients that I have a background as a homeopath, unless they specifically asked about it. If I had started out by telling them that I have such a background, then that might have reduced the likelihood of patients feeling free to express any negative experiences about the treatment. I did however respond honestly if any patients asked me if I have a background as a homeopath. Out of the 33 patients, two asked about my background, upon which I confirmed that I am also a homeopath. I did however point out that I did not treat any of the patients in the research project.

Although the themes have been developed by me and do not "emerge" out of the interviews (Ely et al. 1997), the interviews and the coding of interviews were driven by the content of the interviews. During the interviews I focused on posing open-ended questions to encourage patients as much as possible to describe their own experiences with the treatment and their views and understandings of their experiences, without leading them in a particular direction. Interviews would typically start out with questions such as: *"Can you tell me a bit about your health and how it's developed over the past months?"* and *"Can you tell me a little bit about your experiences with the treatment with the homeopath?"*

Typical follow-up questions were along the line of: *"Can you say a little bit more about that?"* or *"So what happened then?"* When patients had described their depression, typical follow-up questions could be: *"Can you describe that a little bit more, what your depression is like?"*

In order to obtain more knowledge about patients' experiences, for example with the consultations with homeopaths, questions could be as in interview 44: *"So when you went to see the homeopath, can you explain a little bit more, what are those consultations like?"* and later in the same interview: *"So when you've been to see the homeopath, what do you feel like during those consultations?"* Key questions to learn from patients' experiences were often repeated at different times during the interview, both in order to seek confirmation of my understanding of patients' descriptions, as well as to learn more in depth about their experiences. Questions could be posed in slightly different ways so as to

try to increase the chance of patients recalling their experiences. In the presented example the terms *"explain"* and *"felt"* were used at two different time points. In the first instance the patient described how the homeopath was thorough in keeping notes during consultations, posing a range of questions, being thorough and appearing to be understanding and caring. When using the term *"felt"*, the patient recalled how the homeopath's questions resulted in bringing back emotions that had been *"pushed into the back of the mind"*, thereby contributing to additional information about patients' experiences. Moreover, my experiences from one interview were brought to new interviews and did thereby assist me in expanding my understanding of patients' experiences. After the first five interviews had been carried out, I met with professor Paul Bissell who is an expert in qualitative research methods, to review the questions included in the research interview guide. Two new suggestions came up during this meeting, to pose follow-up questions at 6 month follow-up interviews, such as how patients think the treatment may be working; and to pose follow-up questions on their experience when taking homeopathic medicines. No major changes were however made and it was therefore not considered necessary to apply for ethics approval for these minor additions.

As pointed out in section 4.2.6 (Trustworthiness of the results from the qualitative interview study), my background may contribute to the research process. I tried to stick to more "neutral" questions, such as in interview 31: *"Can you say a little bit more about what's your experience been?"* and *"Have you had any changes in your health over these months since you started that treatment?"* When patients had described some of their experiences, and these descriptions were mainly positive, I also posed questions also about their negative experiences. In interview 31 this included: *"Is there anything that you have found during the consultation with [the homeopath] that was strange in any way?"* and *"Is there anything in the interviews that have been difficult or challenging?"* as well as *"Is there anything that you felt was uncomfortable?"* Upon posing these questions, the patient gave a quite detailed description, also explaining that she found the consultations to *"go deeper"* than what she had expected, that she had had a *"bad week"*, and that she could sometimes find it difficult to express herself.

Patients were encouraged to feel free to describe their experiences and I regularly confirmed my understanding of their descriptions through both verbal and non-verbal communication. Member checking was used by "sending back" what I had understood, in

order for patients to correct or confirm my understanding, as well as taking the opportunity to expand my understanding of their experiences, as illustrated by the following questions I posed in interview 31: *"[So] you took one remedy and nothing happened. Took a second and nothing happened. A third and nothing happened and a fourth and nothing happened. What was going through your mind as nothing was changing?"* and interview 36: *"You were saying that you said to [the psychiatrist] you felt that it was helping you more to go and talk to [the homeopath] than to talk to him. If you say a little bit about that. What was the difference?"*

The data has been assessed and reassessed several times. Coding was carried out during and after interviews, and interview transcripts were returned to numerous times. As new interviews were carried out, attention was paid to new arising issues, as well as similarities and differences to issues identified in previous interviews. I considered posing questions related to themes from previous interviews, in order to try to identify any further understandings of these themes, or to identify any opposing views. Thematic analysis was used to allow for flexibility in the process of data analysis, during and after interviews. Analysis followed an iterative approach and it was in part carried out during the interview, by identifying issues arising from participants' responses. Analysis was however mostly carried out after interviews.

A second researcher (CR) checked a random selection of interviews during the last stage of analysis and found coding to be appropriate. Analysis was carried out in several phases. Over 2,000 codes were arranged in groups of 251 codes, which were then reduced to 228 codes. These codes were then placed in the different categories reporting on what patients reported about their understanding, experience, knowledge, beliefs, expectations, hopes and attitudes prior to and at the onset of treatment, and in the documents used as the basis for the results of patients' descriptions following 6 months of treatment. A single quote could be used in more than one category. A total of 150 different versions of draft documents were developed as part of the process of analysis where codes were changed, copied and moved between the different groups of themes, and where themes were revised several times. Throughout the entire process, interviews were returned to whenever needed for confirmation, expansion, refinement or rejection of codes and themes, most frequently in the first stages of the process and less frequently towards the end of the analytic stage.

The developed themes are illustrated with the use of quotes from all 33 interviewed patients. Quotes from several patients were used to contribute to the development of each theme. Patients were most often quoted five times (11 patients), four (8 patients) or three times (5 patients). Eight patients were quoted from six to ten times, and one patient was only quoted twice. The difference in frequency is partly the result of patients providing fuller and wider descriptions of themes, but patients who were quoted seven times or more were also interviewed twice (1-2 months and 6 months), and all patients who were quoted only two or three times were interviewed only once. All themes were developed with the use of several quotes, although some sub-themes and characteristics describing sub-themes were only mentioned by a few patients. In these cases this has been pointed out while describing the results.

Throughout the interviews and the analytical process I attempted as much as possible to avoid posing questions and developing codes and themes that would fit in with any predetermined concepts. This is difficult to avoid entirely and I was fully aware that I have used terms such as "holism" and "the principle of similars" for many years, both in my clinical practice as a homeopath and when teaching homeopathy to students. "Holistic treatment" was developed as part of a theme, but only after having carefully considered whether it could be said with some confidence that this theme was representative of what patients expressed. The other part of the theme, "condition-specific treatment" was however a term I did not expect. I nevertheless developed this theme as it represented what I understood from patients' descriptions. Moreover, "the principle of similars" was only briefly mentioned by very few patients and not described in sufficient detail to form the basis for development of a theme.

The main focus throughout the interviews and the analytical process has been to represent patients' experiences as reported by them. I have aimed to develop themes which are easily understandable, which I found were predominantly represented in interviews and described with a fair degree of rich descriptions, to a large extent by quoting patients directly in text. Moreover, opposite and differing views and experiences have been included where this was found, and themes represent short- and long-term experiences, and what could be perceived as positive as well as negative experiences have been investigated and reported.

In summary, it is my view and hope that the presented themes give justice to patients' descriptions of their experiences with treatment provided by homeopaths. Other researchers might very well have analysed interviews differently and might have come to somewhat different conclusions. The developed and described themes may nevertheless contribute by expanding existing knowledge about depressed patients' experiences with homeopathic treatment. Whether results are generalisable to other contexts needs to be determined in future research and by other researchers. The transferability needs to be considered by different interest groups, in particular patients and clinicians.

6.11 Patients' experiences with treatment provided by homeopaths: Summary

Patients' descriptions of their experiences, knowledge, beliefs and understanding after having undergone treatment provided by homeopaths contributed to the development of themes in four areas: the consultation; homeopathic remedies; changes in their state of health; and their knowledge, beliefs and understanding of homeopathy. All patients primarily described consultations with a homeopath as a positive experience. They commonly described ***feeling listened to***, ***understood*** and ***accepted,*** contributing to the development of the theme of ***CARING SUPPORT***. Patients felt supported by the homeopath, who they also perceived as a warm, friendly and caring person. It was considered important that the homeopath was an ***independent person***, someone who they perceived as a "neutral" person who they could confide in, and who was not a friend or family member who might not understand them and who they did not wish to burden with their problems. However, the ***independent person*** should not be any stranger, but someone who patients described as appearing ***competent***, ***sincere and committed***, adding up to the theme of ***TRUST***. Although some patients had some ***concerns*** about the treatment, such as the lack of information provided by homeopaths, they mostly had no concerns or their concerns were not sufficient to considerably reduce their ***TRUST*** in the homeopath, although some patients expressed doubts of the effect of homeopathic remedies. Patients also described homeopaths as appearing optimistic, positive, encouraging and enthusiastic, adding up to the theme ***OPTIMISM***, increasing their hopes for the treatment, which they had described during the first interview.

The themes ***CARING SUPPORT*** and ***TRUST*** both contributed to patients ***OPENING UP AND UNLOADING***. Patients felt free to tell their stories and express their worries, and this gave them a sense of relief, a "burden off their shoulders". The consultations involved a dialogue with their homeopaths which also made them "think deeper", recall forgotten memories and some patients also came to realisations about their mood, their health and life situations, all contributing to the theme ***REFLECTION AND REALISATION***.

Consultations with homeopaths resulted in patients being prescribed homeopathic remedies. Patients described the ***FORM AND AMOUNT*** as well as the ***PROCEDURES FOR TAKING HOMEOPATHIC REMEDIES***. Their descriptions differed in some respects to what they might be used to when taking conventional drugs, such as not touching the remedies, taking them apart from meals, and avoiding certain substances such as coffee and mint. Although very few patients specifically point it out, it may be that some of these issues contributed more considerably to another theme – ***CREDIBILITY***. Patients did however mention issues such as the dilute nature of homeopathic remedies, the small amount of medication they were instructed to take and criticism they had heard about homeopathy in the media, as factors contributing to ***uncertainty about the credibility*** of the intervention. The same could be said about patients' ***uncertainty*** about the working mechanisms. This ***uncertainty***, together with the understanding that the treatment might work as the result of the combination of homeopathic remedies and consultations, as well as the realisation that external factors may affect patients' health, contributed to the theme ***UNCERTAIN AND COMPLEX WORKING MECHANISMS***. These themes, which are based on patients' reflections about the treatment, showed how patients had developed their knowledge, beliefs and understanding of homeopathy from treatment start to the time of the 6 month interviews. Patients initially had little knowledge or only presented a limited number of assumptions about the treatment. This had developed to more elaborate descriptions, mainly based on what they had experienced. Their developed understanding included treatment being ***holistic*** or ***condition-specific***, and also either ***complementary or alternative*** to ongoing conventional treatment, thereby contributing to the development of the theme ***ADAPTED TREATMENT***.

The most commonly described change in patients' state of health was ***IMPROVED MOOD***, described in a variety of ways such as "feeling less depressed", "happier" or "a dark cloud lifted". These improvements were by some patients described as continuous and by others

more temporary. Other themes developed on the basis of patients' descriptions of changes in their state of health included ***IMPROVED WELLBEING AND ENERGY*** and ***FEELING MORE BALANCED***. Improvements also contributed to ***IMPROVED COPING***, which involved improved ability to cope with everyday life, reduced degree of isolation and an increase in social activities, as well as reduced self-harm and improved self-care. Other patients described ***LITTLE OR NO CHANGE*** and some also ***ADVERSE EVENTS AND FEELING WORSE***. ***ADVERSE EVENTS*** were mostly mild, although some were experienced as moderate or severe, but all were transient and none were diagnosed as diseases. Some patients described an improvement in their state of health following the ***ADVERSE EVENT***, which could be considered to be what homeopaths term a "homeopathic aggravation", which is a part of patients' "healing process". Patients who experienced ***NO CHANGE OR FEELING WORSE*** described this as taking place in spite of, rather than because of, the treatment provided by the homeopath.

7 Mixed methods: The joint results from the pragmatic trial and the qualitative study

The mixed methods approach combines the results of the trial used to assess the acceptability, the safety and the effectiveness of treatment provided by homeopaths with the results of the qualitative study exploring patients' experiences with the treatment. Following the analyses of the quantitative and qualitative data, a comparison was carried out to consider the extent of *convergence*, *complementarity*, or *discrepancy* and *dissonance* (section 4.3.2: The use of triangulation to learn from patients' experiences).

7.1 The acceptability of the intervention

Data from the trial and the qualitative study can, when combined together, help us better understand reasons why some patients accepted and others declined the offer of treatment provided by a homeopath. Sixty percent of patients offered treatment provided by a homeopath, did not take up the offer and receive treatment (trial data). One of these patients said he did not believe in homeopathy. Data from interviewed patients add to our understanding of why this and other patients may have turned down the offer of treatment (*complementarity*). Some interviewees described issues that made them feel uncertain about the credibility of homeopathy, such as the dilute nature of homeopathic remedies and criticism published in the media. More importantly, most interviewed patients said they did not know much or anything about homeopathy and what they could expect. They did however remain open-minded and had hopes that their state of health would improve and some also had altruistic motives for participating. This may explain the reasons why 40 % of patients accepted the offer and had treatment with a homeopath. It is also not unlikely that some or several of the patients who turned down the offer did not know anything about homeopathy or they did not have attitudes and hopes as those described by interviewed patients.

Some data trial and qualitative data was also *convergent*, i.e. data from one method confirmed the findings of the other. Unsuccessful past experience with homeopathic treatment was a reason given by one patient who declined the offer of treatment (trial data) and such experience was mentioned by one interviewed patient (qualitative data). Thinking

homeopathy could not improve the state of health due to negative life circumstances was an explanation given by another patient who declined the offer and some interviewed patients who did not improve during the course of treatment.

7.2 The safety of the intervention

Although mixed methods were originally only planned to be carried out at the reporting stage (section 4.3.2: The use of triangulation to learn from patients' experiences), this also took place at the analytical stage for safety data. Adverse events reported by homeopaths in the trial were jointly analysed with results from qualitative interviews, and the two methods provided an opportunity to confirm and expand knowledge and understanding of adverse events. Three adverse events were identified using both methods (*complementarity*) (table 19: Adverse events in patients treated by homeopaths during the trial).

There was also clear *discrepancy* between trial and qualitative data, as homeopaths reported a significantly lower proportion of adverse events compared to events identified through qualitative interviews. Four to five months into the trial homeopaths had only reported two adverse events, as the guidelines they had been provided only instructed them to report serious adverse events and they assumed that they should only report adverse they considered to be linked to the treatment, whereas assessment of causality was supposed to be made by the researchers. However, changing the procedures at this stage by asking them to report all adverse events did not considerably increase reports of adverse events, as homeopaths overall only reported adverse events that researchers considered to be at least possibly linked to the treatment in 5.4 % of patients, whereas such events were identified in 30.3 % of patients interviewed in the qualitative study.

Neither homeopaths' reports nor qualitative interviews identified any life-threatening events considered to be at least possibly linked to the treatment and all adverse events were transient, thereby showing *convergence* between qualitative and quantitative data.

7.3 The effectiveness of the intervention

Instrumental variables and per protocol analyses of treatment provided by homeopaths for patients with self-reported depression on average resulted in at least a moderate effect on depression and anxiety scores 6 months into the trial. Results did however show wide confidence intervals, ranging from a very small or almost no effect, to an effect size somewhere between moderate and large. The variation in results corresponds to the variety of descriptions obtained through the qualitative interview study (*convergence*). Some interviewed patients described little or no change in their depression and anxiety levels, whereas others experienced a clearer effect and some felt they were no longer depressed or anxious at all.

According to trial data patients treated by homeopaths on average had about 2–3 point lower depression scores than patients in the "No offer" group, but their overall depression scores improved by about 5.5 points (from 16.9 points at baseline to 11.4 points at 6 months). Patients in the "No offer" group improved on average by 2.8 points in the same time period. Hence, a 2.5–3.0 point improvement was seen in both groups and must have resulted from reasons other than treatment provided by homeopaths. A similar trend was seen for anxiety (patients treated by homeopaths improved by an average of 4.6 points, patients not treated by 2.1 points). It is not possible to determine the extent to which individual external circumstances such as other treatment, fluctuations in depression, regression to the mean effects and changes in everyday life circumstances positively affected patients' depression and anxiety scores. However, some patients in the qualitative study acknowledged that it could be difficult to understand the complexity of factors influencing their health, and some also described how they thought life circumstances and the use of other treatment such as antidepressants positively affected their mood. In this respect, data from the qualitative study offered some explanation for the improvement that was seen in both groups (*complementarity*).

The qualitative study provided additional insight and a more nuanced understanding of patients' experiences with treatment provided by homeopaths, and does therefore add to the knowledge gained through the trial (*complementarity*). The depression and anxiety outcomes used in the trial include questions about patients' energy, sleep, appetite, concentration, irritability, restlessness and feelings of stress, which were all described by

some patients in the qualitative interview study. However, only overall outcome scores were assessed in the trial, interpreted as measures of depression and anxiety. Comparison of responses to individual outcome measure questions, with interviewed patients' descriptions, might have provided additional understanding of patients' experiences. Patients in the qualitative study also described symptoms not covered by the trial outcome measures, such as improvements in headaches and other types of pain, vertigo, cramps and menstrual periods. Interview patients also gave more nuanced descriptions of improvements in depression (e.g. feeling happier or a dark cloud that lifted), improved wellbeing and energy, feeling more balanced, and improved coping.

Trial data showed that consultations with homeopaths were fairly long (about one hour). This corresponds to patients' descriptions of homeopaths taking time to listen to them (*convergence*). This was also true for the variety in the length and frequency of consultations, as well as the variety of homeopathic remedies prescribed for patients, which in the qualitative interviews were described as adapted treatment. Qualitative interviews also provided descriptions of patients' experiences with the treatment that were not assessed in the trial. This included feeling supported, trusting the homeopath, opening up and telling their stories to their homeopath and thereby feeling they unloaded or "got things off their shoulders", reflecting and coming to realisations they had not thought of before, and homeopaths' optimism.

7.4 Mixed methods: Summary

The use of a mixed methods approach showed that some of the data collected in the trial was supported by data from the qualitative study, and vice versa (convergence), and in other cases the two approaches complemented each other. This provided an insight into why some patients may have turned down the offer of treatment provided by a homeopath, for reasons such as lack of knowledge about homeopathy, issues reducing patients' trust in the treatment, and a belief that difficult external life circumstances preclude improvements in depression. Patients who accepted the offer of treatment were typically open-minded and hopeful about the possibility that their state of health might improve. All the identified explanations could be used in future research to consider why some patients are interested

in being treated by a homeopath and others are not, and the extent and way in which this influences outcomes.

The use of mixed methods at the analytical phase helped identify an important discrepancy in adverse events reported by practitioners, compared to those identified through qualitative interviews. These findings suggest improved safety guidelines and training would be advisable for homeopaths treating depressed patients. Data from both the trial and the qualitative study suggested homeopathic treatment might result in strong pain, although all adverse events were transient and none were life-threatening.

For assessment of the effectiveness of treatment provided by homeopaths, the mixed methods approach helped confirm the wide variety of improvements experienced by patients, ranging from no improvement at all, to significant reduction in depression and anxiety. It also helped to show that although some improvement was connected to the intervention, patients also improved for other reasons. Qualitative data provided a much more nuanced insight into patients' experiences with the intervention, including improvement in their complaints and their experiences with consultations with homeopaths.

8. Discussion and conclusions

The aims of this thesis were to assess the acceptability, the safety and the effectiveness of offering treatment by homeopaths for patients with self-reported unipolar depression as an adjunct to usual care, compared to usual care alone, and to further explore patients' experiences with this treatment. A mixed methods approach, a pragmatic trial using the "cmRCT" design and a qualitative semi-structured interview study was used to address these aims.

8.1 Summary of results

Forty percent of patients with self-reported depression accepted an offer of treatment provided by a homeopath. The trial over-recruited patients. The main analysis showed a small effect on depression of the offer of treatment, compared to usual care alone. A medium effect size was found in the analysis of received treatment. Some transient adverse events were identified and there was no evidence to suggest treatment was not safe. Key themes were identified through the qualitative study such as "caring support" and "improved mood".

8.2 Strengths of the thesis

8.2.1 Timeliness of the research

In order to ensure the timeliness of this research, an existing published review of "Homeopathy for depression" (Pilkington et al. 2005) conducted in 2004 was updated. The updated review adds evidence suggesting homeopathic remedies may be more efficacious than placebo and comparable to antidepressants. Evidence from uncontrolled studies indicates a significant proportion of depressed patients feel better after treatment provided by homeopaths. In spite of the identified research in this area, the review identified no pragmatic trials or qualitative studies assessing treatment provided by homeopaths for patients with depression. Given the prevalence of depression in the UK, the prevalence of depression treated by UK homeopaths, and the fact that homeopathy is provided through the UK's publicly funded health system (NHS), this research addresses a timely question.

8.2.2 Innovation in research

This doctoral work covers a number of innovations. This thesis reports the first pragmatic trial and qualitative study assessing individualised treatment provided by homeopaths for patients with self-reported depression.

Although there are many trials of antidepressants, no trials of treatment by a clinician prescribing an oral medication for depression were identified. Therefore, it is possible that this is the first trial which tests the effectiveness of a combination of consultations with a clinician and orally prescribed medication.

This thesis also reports the first mixed methods study carried out in this field. This approach helped confirm results in the trial with results of the qualitative study, and vice versa; and it provided additional insight into the safety of the treatment.

8.2.3 The challenge of conducting research into homeopathy

Multiple challenges were encountered and overcome during the design and conduct of this research.

Homeopathy in the media and the scientific literature

Considerable debate and controversy surrounds homeopathy in the UK. Although some UK media report positive views of homeopathy including "success stories" (e.g. Collins 2014, BBC 2014), the majority of media coverage over the past decade has been highly negative, for example in The Guardian (Ernst 2015, Sample 2007), The Telegraph (Palmer 2009), Herald Scotland (Puttick 2013), and the BBC (2010). Examples of remarks made in UK and international media include: "*Homeopathy […] is much more like religion than science*" (Davidson 2014, para. 5 of 16), and (Harvey 2015, para. 3 of 35): "*Naturopaths are quacks. So are chiropractors, traditional Chinese herbalists, iridologists, palm-readers, homeopaths […] Quack, quack, quack.*"

Although some scientific literature is balanced, presenting e.g. opposing views on whether doctors should recommend homeopathy (Fisher & Ernst 2015), and whether NICE should

fund CAM and homeopathy research (Colquhoun 2007, Franck et al. 2007), the majority communicates highly critical views and opinions about homeopathy. There are repeated statements such as *"[…] it is indisputably proven that homeopathy has no action beside a possible placebo effect*" (Garattini et al. 2013, p.1). Some researchers oppose the idea of keeping an open mind to homeopathy (Baum & Ernst 2009, p.973): "*To have an open mind about homeopathy […] is therefore not an option*." Calls have been made for the UK Government to stop funding homeopathy in the NHS (Baum 2010). Individual homeopaths, manufacturers of homeopathic remedies, and homeopathy organisations have all been criticised for making incorrect or inappropriate claims about treatment (Ernst 2010b, Jones & Ghosh 2011). Campaigns referred to as "witch hunts" have been set up to remove University homeopathy Degrees (Colquhoun, in: Moynihan 2012, p.1): "*I've got no mercy for vice chancellors and senior medics. I don't mind going for the jugular, because it's a betrayal of what universities are for, it's going back to pre-enlightenment*."

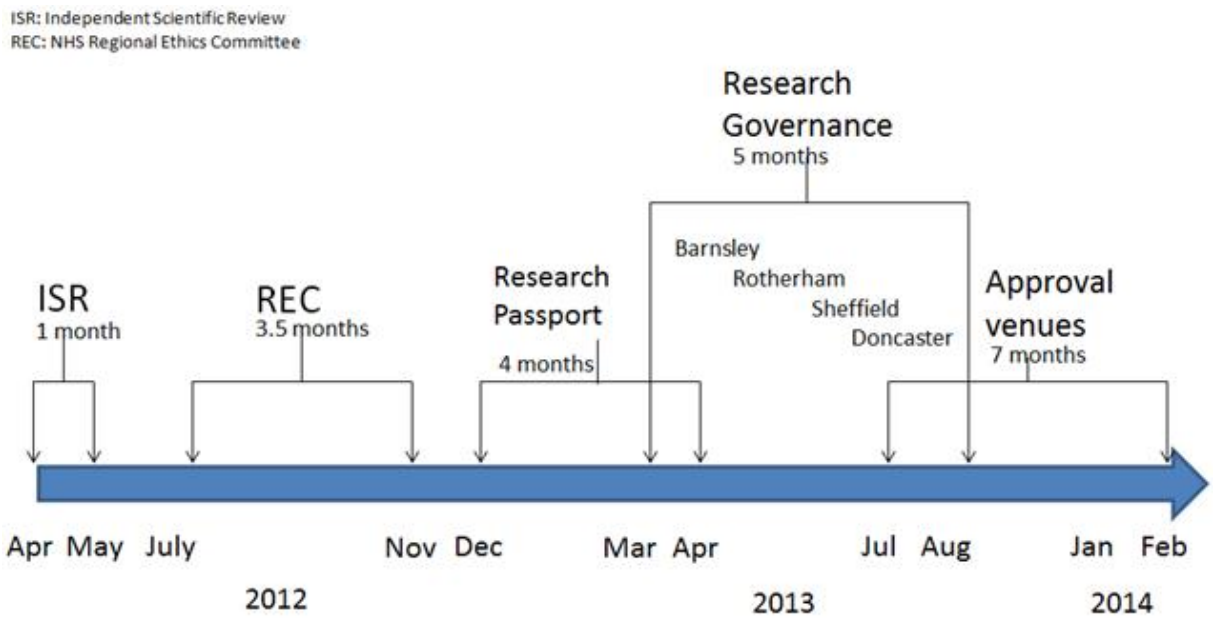
The process of obtaining research permissions

It took 23 months in total to obtain all permissions required to start the research project. The different parts of this process are presented in Figure 9 (The stages of the ethics and governance procedures). This time length is not unusual (Dilts et al. 2006). This project had the additional challenge of obtaining approval in a climate where many people think that homeopathy should not be researched. Below follows a description of our experience with one particular (now disbanded) NHS Research Ethics Committee (REC) (NRES Committee Yorkshire & The Humber – Leeds Central).

Following online submission for ethics approval through the Integrated Research Application System (IRAS), I was invited by the REC to attend their review meeting. However, after a prolonged waiting period in the corridor, my supervisor (Dr Clare Relton) and I were informed by an assistant that the Committee would not meet with us as they thought that by just allowing us into the REC room they would be endorsing homeopathy research. We were informed that the Committee were going to seek the opinion of the National Research Ethics Service (NRES) before considering the application. We were shown excerpts from the House of Commons Science and Technology Committee report on homeopathy which considered further research in homeopathy not to be justified (2010, §§77–78). The REC would not change its decision in spite of our referral to the

Government Response (2010, §§19–21) stating that according UK principles for public research funding, further research cannot be categorically ruled out, each application should be assessed on its own merits, and proposals for research contributing to clarifying the impact of homeopathy should be considered. The REC would not change its decision, despite the fact that I had travelled to the meeting from abroad and we offered to answer any questions the Committee might have not related to the homeopathy aspects of the project.

Figure 9. The stages of the ethics and governance procedures



A month later the Committee informed us by letter that they had come to the conclusion that the study should be classified as a Clinical Trial of an Investigational Medicinal Product (CTIMP), and that their particular REC was not recognised to review CTIMPs and they therefore requested us to withdraw our application and resubmit to another REC.

After absorbing the shock of being invited and then uninvited to the RECT, we then decided to file a complaint to the Director of the National Research Ethics Service (NRES) (http://www.hra.nhs.uk/documents/2013/09/01-13-lii-nres-complaints-register-2012-2013.pdf). We also asked NRES to determine whether the research would classify as a CTIMP and explained that it was not a trial testing homeopathic remedies, but the acceptability, safety and effectiveness of the offer of treatment provided by homeopaths. We received a formal apology from the Director of NRES for the refusal to see the Committee, my travel expenses were refunded, and the REC was instructed that this was

not a CTIMP, and to assess the application without further delay. The REC application was approved one month later, with one minor amendment; that patients understood that any standard medication would be continued as prescribed by their GP/specialist.

Following the REC approval process, there was a lengthy process whereby research management applications were assessed by the four health authorities in each region (Barnsley, Doncaster, Rotherham, Sheffield), and the final stage was that each clinic had to consider the research project and grant their permission. After direct contact and contact through other researchers with several GP clinics, two agreed to offer rooms for consultations to take place, as well as three "integrated medicine" clinics (CAM and conventional).

The application procedure was unnecessarily prolonged due to inappropriate and incorrect Committee decisions which were in part due to the anti-homeopathy climate.

The funding for this research was raised from multiple sources, including an independent foundation providing research funding for various projects, homeopathy users, individual homeopathy practitioners and homeopathy research foundations, practitioner organisations and a manufacturer, and some funding was also obtained from UK sources, including a small amount from the NIHR senior investigators' funding.

One strength of this thesis is that it demonstrates that despite these challenges, it is possible to fund and conduct research into homeopathy in the UK, and that it is possible to gain the approvals required to conduct research into this in an NHS and an academic setting.

8.2.4 The feasibility of the research design

A further strength of this research is the use of the recent "cmRCT" design. This design facilitated the quick and efficient identification, and complete recruitment of more than the required sample size and the required sample of people with need – those with self-reported depression. This is particularly good in light of only one third of UK trials, including trials in mental health, reach recruitment targets on time and almost half recruit less than 80 % of the number of participants needed (Bower et al. 2007, McDonald et al.

2006). Under-recruitment has also been a problem in homeopathy in depression trials (Adler et al. 2013), including a UK trial (Katz et al. 2005).

Moreover, the 6-month questionnaire response rate was higher than expected, thereby allowing for statistical analyses to be carried out with no loss of power. Patients randomly selected to the "No offer" group in trials using the "cmRCT" design are not told the "disappointing news" that they have been selected not to receive the tested intervention. Drop-out due to resentful demoralisation (Torgerson & Torgerson 2008) is therefore avoided. This is also more similar to regular practice, where patients would normally not be told about treatments that they are not then able to receive.

8.3 Limitations of the thesis

8.3.1 Short term results for a long term condition

Although 6 month results suggest there was a small effect of the offer of treatment and a medium sized effect of treatment received, wide confidence intervals preclude firm conclusions from being drawn. Although this was 6 months into the trial, the treatment period was only three to four months. The 12 month results may provide clearer indications of the (non)-effectiveness of treatment by homeopaths, with smaller confidence intervals. It is also possible that analyses of sub-groups of patients could have offered clearer results. For example, variations in patients' depression scores at baseline would be much smaller if only patients with e.g. moderate depression assessed, compared to the full sample. This would give much smaller standard deviations, which might contribute to larger effect sizes. No post-hoc tests were however carried out, as this could be considered data dredging and contribute to risk of bias (Altman 1991, Machin et al. 2007).

8.3.2 Effects of individual elements of the intervention

Some audiences may criticise the fact that this research does not address the question as to whether or not homeopathic remedies are placebos. Although this is an interesting question, this thesis addresses a different question – that of the effectiveness of the "whole treatment package" including consultations with a homeopath and the prescription of

individualised homeopathic remedies as an adjunct to usual care. This question required a pragmatic trial design with treatment as usual as the comparator (Relton et al. 2010). Although they are less common (Vallvé 2003, in: Treweek & Zwarenstein 2009), pragmatic trials are better suited than explanatory trials to inform clinical practice and health policy decisions (Patsopoulos 2011, Thorpe et al. 2009, Tunis et al. 2003).

Having said this, it is still relevant to consider the effect that the individual elements of the intervention may have had on the outcomes. Some of these elements are by some described as "non-specific" or placebo effects (Novella 2010). Placebo effects have been considered to be any effects not resulting from the tested drug (Benedetti et al. 2014). Others have criticised the "placebo" concept, pointing out that no clear and agreed definition of "placebo" exists (Nunn 2009). Nunn (2009, p.1015) also questions how placebos can be considered to have non-specific effects, as effects that cannot be specified are difficult to identify; and if effects can be identified, then they should be considered specific effects. Rather than getting caught up in the placebo/non-placebo debate, it might be more useful to assess the potential elements that may have influenced the outcomes in the pragmatic homeopathy depression trial, and refer to them as they have been presented. This section therefore explores what results that may potentially be attributed to the consultation, the patient-practitioner relationship, patients' expectations and hopes, disclosure, conditioning, patient enablement and specific effects of homeopathic medicines.

The consultation and the patient-practitioner relationship

As suggested in section 3.1 (What is homeopathy?) homeopathic treatment has some resemblance to psychological interventions, in particular compared to the person-centred approach. This involves basic conditions for patients to improve, including unconditional positive regard, empathic understanding and congruence; aspects that are also commonly seen in homeopathic treatment (Kaplan 2001, Townsend 2002). These concepts, and in particular empathy, have similarities to "caring support," one of the themes developed in the qualitative study assessing patients' experiences with treatment provided by homeopaths. The theme resulted from patients' descriptions of being given a considerable amount of time to present their problems, feeling listened to and accepted by their homeopath, who they perceived to be warm and friendly, respectful, non-judgmental and understanding (section 6.9: Depressed patients' experiences with treatment provided by

homeopaths). These aspects positively influence the patient-practitioner relationship and it is plausible that this may affect patients' mood.

Patients' expectations and hopes

Another important aspect to consider when assessing patients' outcomes is expectation. Practitioners' empathy and patients' expectations were recently found to be positively correlated to depression outcomes in a pragmatic trial assessing another CAM therapy – acupuncture (MacPherson et al. 2013). Other research did however suggest that there was no correlation between patients' expectations of homeopathic treatment and their outcomes (Thompson & Weiss 2006).

Although expectation was not examined in the pragmatic homeopathy depression trial, in the qualitative interview study, patients commonly stated they did not have any expectations as they knew very little or nothing about homeopathy, but most of them expressed hopes that their condition would improve (section 6.8: Expectations, hopes and attitudes at treatment start). Patients' hopes may also have been strengthened through the practitioners' expressed optimism. The hopelessness that depressed patients commonly experience might thereby be replaced by hopefulness.

The patient-practitioner relationship and patients' feeling of hopefulness may also have been influenced by the extent to which patients trusted their practitioner. When describing their homeopaths, patients in the qualitative study used words such as: sincere, committed, genuine, thorough, persistent and competent (section 6.9.1: Experiences with the consultation). Although some said they did not understand how homeopathy worked and they felt uncertain about the credibility of the treatment, most had no concerns about the treatment and overall patients trusted their practitioner (section 6.9.3: Knowledge, beliefs and understanding of homeopathy).

Disclosure

As mentioned in section 3.1 (What is homeopathy?), disclosure has been found by others to positively contribute to patients' mental state of health (Thompson and Weiss 2006). In the qualitative study patients described feeling able to open up and unload their worries

and concerns (section 6.9.1 : Experiences with the consultation). This is also likely to positively have affected patients' mood.

Conditioning effects

Conditioning effects, i.e. effects of treatment resulting from previous experience with the intervention, can also strengthen "non-specific" effects (Kong & Benedetti 2014). This was however less probable in the homeopathy depression trial, as very few patients reported having any relevant past experience with the intervention.

Patient enablement

Another theme developed in the qualitative study was "reflection and realisation" (section 6.9.1: Experiences with the consultation). Patients described thinking carefully about their current and past life experiences and in some cases this helped bring back forgotten memories. This could possibly contribute to enablement – which refers to an improvement in patients' ability to understand and cope with their complaints. Enablement has been found by other researchers to affect long-term results in homeopathic treatment (Bikker et al. 2005, Mercer 2005).

Effectiveness of homeopathic medicines

As this was a pragmatic trial, it did not test the specific effects of homeopathic medicines per se. In the qualitative study some patients stated they felt homeopathic remedies had an effect and others did not feel they improved from taking these medicines, whereas most expressed uncertainty as to which part of the treatment they felt was of benefit (section 6.9.3: Knowledge, beliefs and understanding of homeopathy). Some researchers have suggested that the effect of treatment by homeopaths may be the result of synergistic effects of the consultation and the medicines (Milgrom 2008, 2012, Thompson & Weiss 2006, Walach 2003, 2005).

What if homeopathic remedies have no specific effect?

Should treatment by a homeopath be recommended for depressed patients if the homeopathic remedies are ineffective? Given that most psychological and pharmacological interventions are not intrinsically effective, then perhaps the answer should be yes. This view was supported by some patients in the homeopathy depression trial who were uncertain as to what part of the intervention helped them improve, but stated that they didn't really care as long as they felt their state of health improved. Walach (2008) suggests that rather than dismissing interventions with so-called "non-specific" effects, such effects should be maximised as they contribute more significantly than the specific effects of interventions.

Summary

Part of the effect experienced by patients is likely to have resulted from the positive patient-practitioner relationship developed in the consultations. This is likely to have included at least the possibility to share thoughts and feelings (disclosure), the feeling of receiving caring support, patients' hopes of improvement which is likely to have been strengthened through the trust patients had in their practitioner and the optimism the practitioner expressed, and the degree to which patients felt enabled to deal with their condition.

8.3.3 Self-reported depression

Another limitation of this study was that depression was self-reported using patient completed outcomes rather than diagnosed by a clinician. Although qualitative interviews suggest that trial participants were hoping for help to improve their mood by participating in the research, patients were not all necessarily treatment seeking. These factors may reduce the generalisability of the results to clinical settings where patients are treatment seeking and have a diagnosis of depression made by their clinician.

It is unclear why the 6-month questionnaire response rate was lower for patients who did not take up the offer of treatment. This could have influenced analyses of results, but there

was little evidence to suggest that these patients were different with regards to any baseline covariates that could affect outcomes.

8.3.4 Interpretation of adverse events

Although the procedures for categorising severity and potential causality of adverse events were found to be feasible in this trial, only two so-called "homeopathic aggravations" were identified. This might be more easily identified had we used guidelines designed by other researchers to consider such effects (Stub et al. 2015).

8.4 Generalisability and comparability to other interventions

The novel design used in this trial for this particular intervention adds some challenges to the generalisability of results. This includes the use of self-reported outcomes instead of diagnosed depression. However, evidence suggests self-reported outcome measures may be more conservative than clinician-rated outcomes (Cuijpers et al. 2010a). PHQ-9 is useful for depression screening, it has high validity and reliability, good sensitivity and specificity, it is comparable to other outcome measures, sensitive to change, and useful for patients with various comorbidities (Kroenke et al. 2010, Löwe et al. 2004a, 2004b, 2006).

Another issue affecting generalisability was that patients were not necessarily treatment seeking. However, patients who consult with homeopaths in regular clinical practice may describe symptoms of depression even though they have not been diagnosed. In this respect, patients in the trial would be more similar to this population.

Moreover, wide confidence intervals limit the possibility to draw firm conclusions and generalise results.

With these limitations in mind, it is suggested that the results of the trial may be generalised to patients with self-reported depression who use treatment provided by a homeopath as an adjunct to usual care.

The generalisability of results of the qualitative study should be considered through additional research and could possibly be assessed in light of qualitative research assessing treatment by homeopaths in other areas than depression.

For assessing the comparability to other interventions, results of research reporting on effectiveness, safety and acceptability will be used.

The effectiveness of homeopathy compared to antidepressants

Even though placebo-controlled trials are fundamentally different to pragmatic trials, comparison of outcomes in placebo-controlled depression trials may be helpful for considering the effect size in the pragmatic homeopathy depression trial.

As reported in section 3.5.9 (Discussion of a systematic review of homeopathy in depression), existing evidence for antidepressants is weak, effect sizes are small (Kirsch 2014, Arroll et al. 2009, Moncrieff et al. 2004), and even similar to placebo effects (Kirsch 2014). The effectiveness of the offer of treatment in the pragmatic homeopathy depression trial (d=0.30) and the treatment received (d=0.57), was at least comparable to the efficacy of antidepressants found in a Cochrane review (Moncrieff et al. 2004) reporting on TCAs (d=0.39) and several non-Cochrane reviews with meta-analyses of various antidepressants (range 0.28-0.39) (Kirsch 2014).

It should also be kept in mind that patients in the homeopathy depression trial may have been "sicker" than patients in trials testing antidepressants. On average homeopathy patients suffered from long-standing depression, they had multi-morbidities, they were taking a wide range of different conventional drugs and were seeing various practitioners for their complaints. Hence, patients in the homeopathy trial were more comparable to the general population of depressed patients than patients in trials testing the efficacy of antidepressants, as these trial participants typically do not suffer from so many co-morbidities and are excluded if they are taking other drugs.

The effectiveness of homeopathy compared to psychological interventions

Results of the homeopathy trial were also comparable to various psychological interventions, which have been found to have effect sizes ranging from 0.14 to 0.67 compared to waitlist, treatment as usual or placebos, and which also report wide confidence intervals (Barbato & D'Avanzo 2006, Bolier et al. 2013, Cuijpers et al. 2010b, Driessen et al. 2015, Huntley et al. 2012, Linde et al. 2015) (details in section 3.5.9: Discussion of a systematic review of homeopathy in depression).

The safety of homeopathy compared to antidepressants and psychological interventions

Assessment of the safety of homeopathy compared to other interventions is possible by comparing the prevalence and severity of adverse events.

The prevalence of adverse events reported in the homeopathy trial appeared to be lower (28% reported, 16% considered at least possibly related to the intervention) than the prevalence of adverse events reported for antidepressants drugs, which has been found to be up to 92 % for some symptoms (further details in section 3.5.9: Discussion of a systematic review of homeopathy in depression). Moreover, adverse events in the homeopathy trial that were considered to be at least possibly related to the intervention were mostly mild and all were transient. In contrast, adverse effects caused by some antidepressants may be serious, such as increased suicidal ideation, risk of stroke, abortion and death. No data was found for psychological interventions to allow for comparison of the safety with the results of the homeopathy trial.

The acceptability of homeopathy compared to antidepressants and psychological interventions

As reported in section 3.5.9 (Discussion of a systematic review of homeopathy in depression) evidence from Cochrane reviews suggested that numbers needed to harm (NNH) resulting in withdrawal from trials ranged from 4-30 for TCAs and 20-90 for SSRIs (Arroll et al. 2009). It is not known that any patients in the pragmatic homeopathy trial dropped out due to any adverse effects.

Results reported through the Improving Access to Psychological Therapies (IAPT) programme (Glover et al. 2010) are used for comparison of the acceptability in the pragmatic homeopathy trial. Data collected from 32 IAPT sites in the UK (140,000 consultations, 75,000 patients) included 29 % who were diagnosed with depressive episodes and 29 % with mixed anxiety and depressive disorder. Their baseline PHQ-9 depression scores were comparable to patients in the pragmatic homeopathy trial. Although no data was presented for the IAPT programme on the proportion of patients accepting an offer of treatment, about 30 % had only a single session with a therapist, with no further follow-up consultations. This was the case for 8 % (6 of 74 patients) included in the pragmatic homeopathy trial, whereas 92 %, 88 % and 84 % had at least two, three or four consultations respectively. This result must also be seen in light of the fact that patients receiving the offer of treatment in the homeopathy depression trial had not self-recruited out of interest in the intervention, but were randomly selected from a large cohort of patients, thereby making the results more generalisable to the general population of patients who self-report depression.

It is also worthwhile noting that qualitative interviews, which were carried out with 45 % of patients who received treatment by a homeopath, suggested only 18 % (6 of 33) had past experience with homeopathic treatment and for at least half of these patients their past treatment experience was significantly different to the treatment they received as part of the trial. According to qualitative interviews, most patients knew very little or nothing at all about homeopathy. Evidence therefore suggests participants were not in general "pro homeopathy" patients. In light of the evidence presented in this section, and in light of the current anti-homeopathy climate in the UK, it would seem fair to conclude that the intervention had a high acceptability rate.

Summary of the comparability with other interventions

In summary, results of the homeopathy depression trial suggest that the effectiveness of the intervention was at least comparable to antidepressants and psychological therapies as reported in various systematic reviews. Patients reported fewer and less severe adverse events compared to antidepressants, and treatment appeared to have a high rate of acceptability compared to antidepressants and psychological interventions.

8.5 Conclusions

This research provides new insights into the acceptability, the safety and the effectiveness of treatment provided by homeopaths for patients with self-reported depression, as an adjunct to usual care, with additional insight into patients' experiences with this treatment.

Despite the somewhat hostile climate to homeopathy and homeopathy research in some areas and the arduous and complex governance processes, after 23 months and one complaint to NRES, all the necessary ethics and research governance permissions to conduct this research in the NHS were obtained.

Using the Yorkshire Health Study research facility and the innovative "cohort multiple" RCT design, the trial over-recruited a representative sample of people with self-reported moderate to severe depression from the South Yorkshire area of the UK. The majority of those recruited reported moderate to high levels of anxiety. They had on average 3 other long-standing conditions and were taking on 4–5 medications (42% used antidepressants).

The treatment was acceptable to a significant proportion (40%) of patients with self-reported depression, who had one or more consultations with a homeopath and individualised homeopathic remedies. Some transient adverse events were reported, although there was no evidence to suggest treatment was not safe.

At 6 months, the "best guess" (mean) using an ITT analysis gives a small effect size (d=0.30) for those offered the treatment. The instrumental variables analysis identified a medium effect size (d=0.57) for those who received the treatment. Similar results were seen for anxiety. Wide confidence intervals do however preclude any firm conclusions from being drawn on the basis of 6 month results and 12 month results should be assessed.

Semi-structured interviews with patients who had received treatment, revealed patients describing "caring support", "trust", "optimism", "opening up and unloading" and "reflection and realisation" when discussing the consultations. Patients most commonly and clearly described "improved mood" as an outcome experienced during the course of treatment, other themes were "improved wellbeing and energy", "feeling more balanced", "improved coping", "physical improvement", "little or no change", and "adverse events

and feeling worse". Homeopathy was understood as an "adapted treatment". Issues were raised regarding the "credibility" of homeopathy, and patients described "uncertain and complex working mechanisms" when trying to understand how homeopathy may work. Mixed methods confirmed results of data from the trial with data from the qualitative study, and vice versa, and additional insight was gained about safety.

Analysis of the 12 months results will hopefully provide more clarity as to the size of any effect of treatment by a homeopath on self-reported depression, as well as the cost-effectiveness of treatment.

8.6 Recommendations

Preliminary results, assessed 6 months into the trial, suggest treatment provided by homeopaths for patients with self-reported depression is acceptable and no evidence suggested it is unsafe. It is somewhat early to assess the results of the effectiveness of the intervention, but results so far are promising. Treatment provided by homeopaths could therefore be considered by clinicians and commissioners allocating funds for homeopathy and for depression treatment to be a potentially helpful adjunct to usual care, in particular for patients with insufficient response to usual care.

NIHR should consider making funding available for further research to be carried out in this field, in particular to assess long-term effects and to carry out cost-effectiveness analyses.

As adverse events were more frequently identified by the researcher than the practitioners, researchers and practitioners (and their professional organisations) should assess and, if necessary, revise existing guidelines to ensure the safety of patients suffering from depression. This should include guidelines for identifying, handling and reporting risk issues and adverse events.

Researchers with real world questions are recommended to consider the use of the pragmatic "cmRCT" design as a means of achieving recruitment goals, reducing attrition

rates, assessing long-term outcomes including cost-effectiveness analyses, and improving generalisability of results.

In future pragmatic trials assessing homeopathy for depression, researchers should consider planning for analysis of sub-groups, for example patients with and within a particular group of depression severity or patients with a higher and a lower rate of long-standing comorbidities, and with or without antidepressant and other drugs. Long-term studies also assessing cost-effectiveness are recommended.

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