

MIRtazapine added to SSRIs for Treatment Resistant Depression in Primary Care: a placebo controlled randomised controlled trial
(MIR)



Trial Identifiers

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Chief Investigator: Dr David Kessler



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1. Trial Management

1.1 Sponsor

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1.4 Trial Centres

Primary Care and Psychiatry centres at four centres led by the following Principal Investigators:

Bristol (lead centre)

David Kessler (GP & Chief Investigator)
Glyn Lewis (Psychiatry)

Exeter

Professor John Campbell (GP)
Professor Chris Dickens (Psychiatry)

Manchester/Keele

Professor Carolyn Chew-Graham (GP)
Professor Ian Anderson (Psychiatry)

Hull/York

Professor Una MacLeod (GP)
Professor Simon Gilbody (Psychiatry)

1.5 Other co-investigators

Professor William Hollingworth

University of Bristol

Professor Tim Peters
University of Bristol

Dr Nicola Wiles
University of Bristol

Dr Simon Davies
University of Toronto

1.6 Collaborators

Dr Barbara Compitus
GP and representative of Bristol Primary Care Trust

Claire Planner
Research Associate, University of Manchester and Liaison with patient and public representatives

1.7 Trial Statistician

Professor Tim Peters, Professor of Primary Care Health Services Research and Head of School of Clinical Sciences

1.8 Trial Committees

1.8.1 Trial Management Group

The Trial Management Group (TMG) will comprise all investigators, the trial manager, research and administrative staff, with input from patient/public representatives.

Members of the TMG contribute to the trial in the following ways: trial design, trial centre recruitment and trial conduct, trial management, trial logistics and cost management, economic evaluation, trial methods, statistical data analysis, and publication.

The TMG will meet approximately monthly to oversee the day-to-day management of the trial. The TMG will be provided with detailed information by the Centre staff regarding trial progress. Most meetings will be by teleconference, but the TMG will also meet face to face once or twice a year.

1.8.2 Trial Steering Committee

The Trial Steering Committee (TSC) will meet once or twice a year.

The membership will include: independent chairperson; three independent members; one/two principal investigators; and one or two patient representatives. Trial co-ordinators, statisticians etc will be invited to attend as appropriate. Observers from the HTA and the sponsor institution (University of Bristol) will be invited to each meeting.

The role of the TSC is to provide overall supervision of the trial on behalf of the HTA. In particular, the TSC will focus on progress of the trial, adherence to the protocol, patient safety and consideration of new information.

The TSC terms of reference can be found in Appendix 1.

1.8.3 Data Monitoring Committee

The Data Monitoring Committee (DMC) will meet twice a year.

The DMC will review the accruing trial data, unblinded if appropriate, and assess whether there are any safety issues that should be brought to participants' attention or any reasons for the trial not to continue.

The DMC will be independently chaired. In addition there will be 2 other members who are independent of both the trial and TSC and experts in the field of the research. The trial statistician may be invited to attend part of the meeting to present the most current data from the trial.

The DMC terms of reference can be found in Appendix 2.

2. Trial Synopsis

Trial title

MIRtazapine added to SSRIs for Treatment Resistant Depression in Primary Care

Phase

Phase IV

Sponsor

University of Bristol

Chief Investigator

Dr David Kessler

ISRCTN

ISRCTN06653773

EudraCT No.

2012-000851-15

REC reference

12/WA/0353**Medical condition under investigation**

Treatment resistant depression

Purpose of trial

To test whether the addition of the antidepressant mirtazapine is effective in reducing the symptoms of depression compared with placebo in patients who have been treated with a Serotonin Selective Reuptake Inhibitor (SSRI) or Serotonin and Noradrenaline Reuptake Inhibitor (SNRI) for at least six weeks

Primary objectives

To investigate in adults ≥ 18 years in primary care with treatment resistant depression (TRD) if the use of mirtazapine, compared with placebo, reduces the symptoms of depression measured as a continuous variable at 12 weeks using the Beck Depression Inventory (BDI).

We will also describe a binary variable using the BDI, representing response, defined as a reduction in depressive symptoms of at least 50% compared to baseline, a widely used definition of improvement

Secondary objectives

In relation to the use of mirtazapine compared with placebo we will also

1. Describe the rate of remission of symptoms, defined as a score on the BDI of less than 10
2. Describe any change on a measure of generalized anxiety, the Generalised Anxiety Disorder & Questionnaire (GAD-7)
3. All of the above outcomes measured at 24 weeks and 12 months
4. Measure antidepressant use and adherence
5. Estimate the cost-effectiveness from the perspectives of the NHS, patients, and society
6. Compare all adverse events including: any new symptoms or worsening of existing symptoms, consultations for a documented deterioration in illness and Serious Adverse Events

Trial design

A two parallel group multi-centre pragmatic placebo controlled randomised trial with allocation at the level of the individual.

Trial participants

Patients in primary care with treatment resistant depression

Outcomes

Primary outcomes:

1. Change in depression symptoms measured as a continuous variable using the BDI at 12 weeks
2. Response in depression symptoms, a binary variable defined as a reduction of at least 50%

Secondary outcomes:

3. Remission of depression symptoms (a score of less than 10 using the BDI)
4. Change in anxiety symptoms as measured using the GAD-7 at 12 and 24 weeks and 12 months
5. Adverse events including consultation for a documented deterioration in illness or hospital admission

(telephone call at 2 weeks, visits at 6 and 12 weeks). We will also include a standard measurement of adverse effects at 6 weeks, 12 weeks and 12 months, a self-report instrument, the Antidepressant Side Effect Checklist (ASEC)

6. Quality of life using the EQ-5D-5L (as recommended by NICE, paper based questionnaire administered at 12 and 24 weeks and 12 months)

7. Number of primary care consultations, by type e.g. face-to-face, telephone, etc. and who seen; and prescribed medication from practice records

8. A questionnaire, administered at 12 and 24 weeks and 12 months, will provide information on: use of other primary and community care services (NHS Direct, attendances at walk-in centres, use of community health care services); secondary care related to mental health (number of out-patient visits, type of clinic, and reason for visit; inpatient stays, length of stay and reason); use of social services and disability payments received; personal costs related to mental health (expenditure on over-the-counter medication, expenditure on prescriptions, travel costs associated with health care visits, loss of earnings, out of pocket expenditure on other services e.g. private counselling or complementary and alternative therapies, child care and domestic help); time off work and unpaid activities

9. Adherence to antidepressant medication, measured using a standardised instrument (Morisky).

Sample size

470

IMP, dosage, route of administration

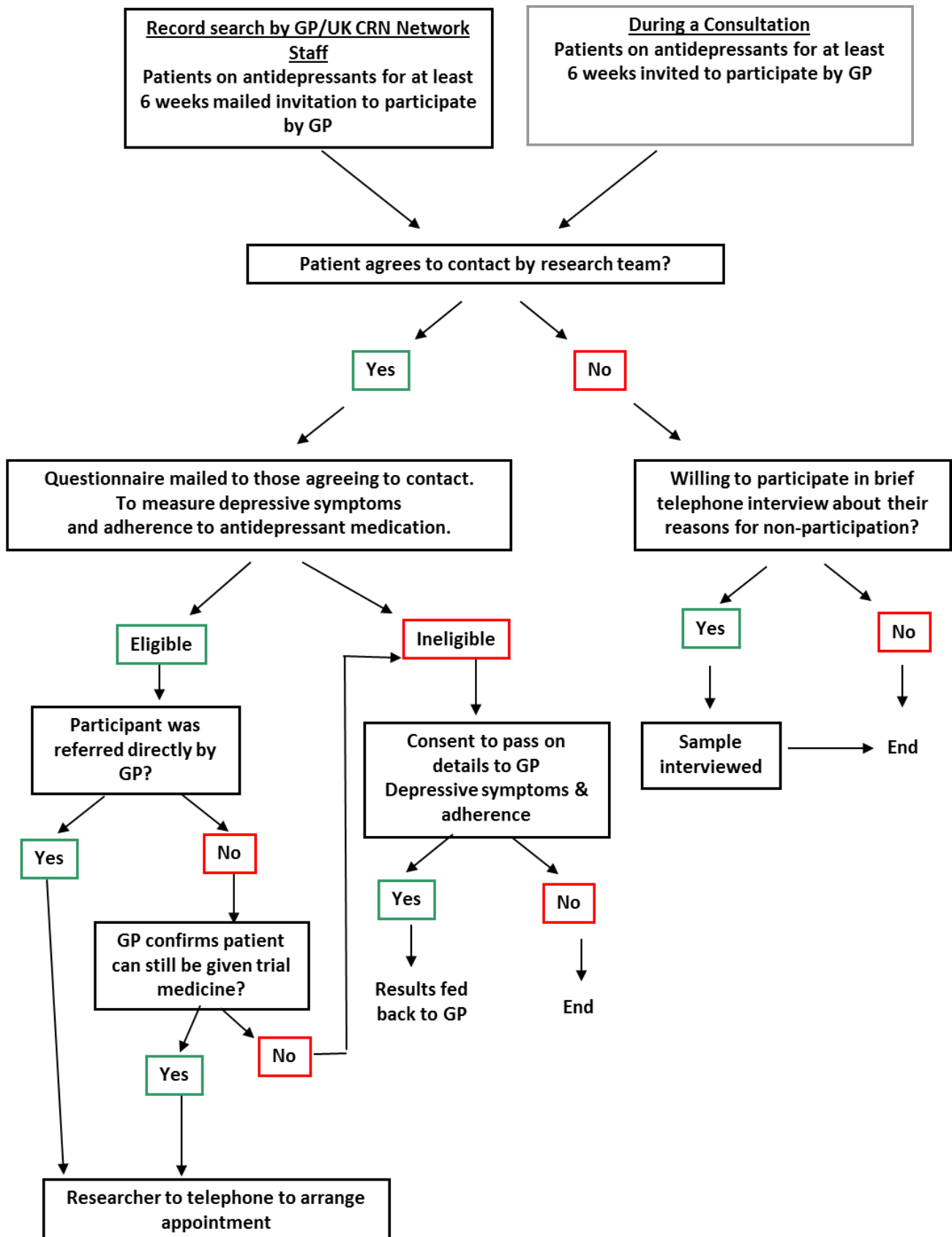
Oral mirtazapine or matched placebo, starting at 15mg daily for 2 weeks and increasing to 30mg daily thereafter

Duration of treatment of a subject

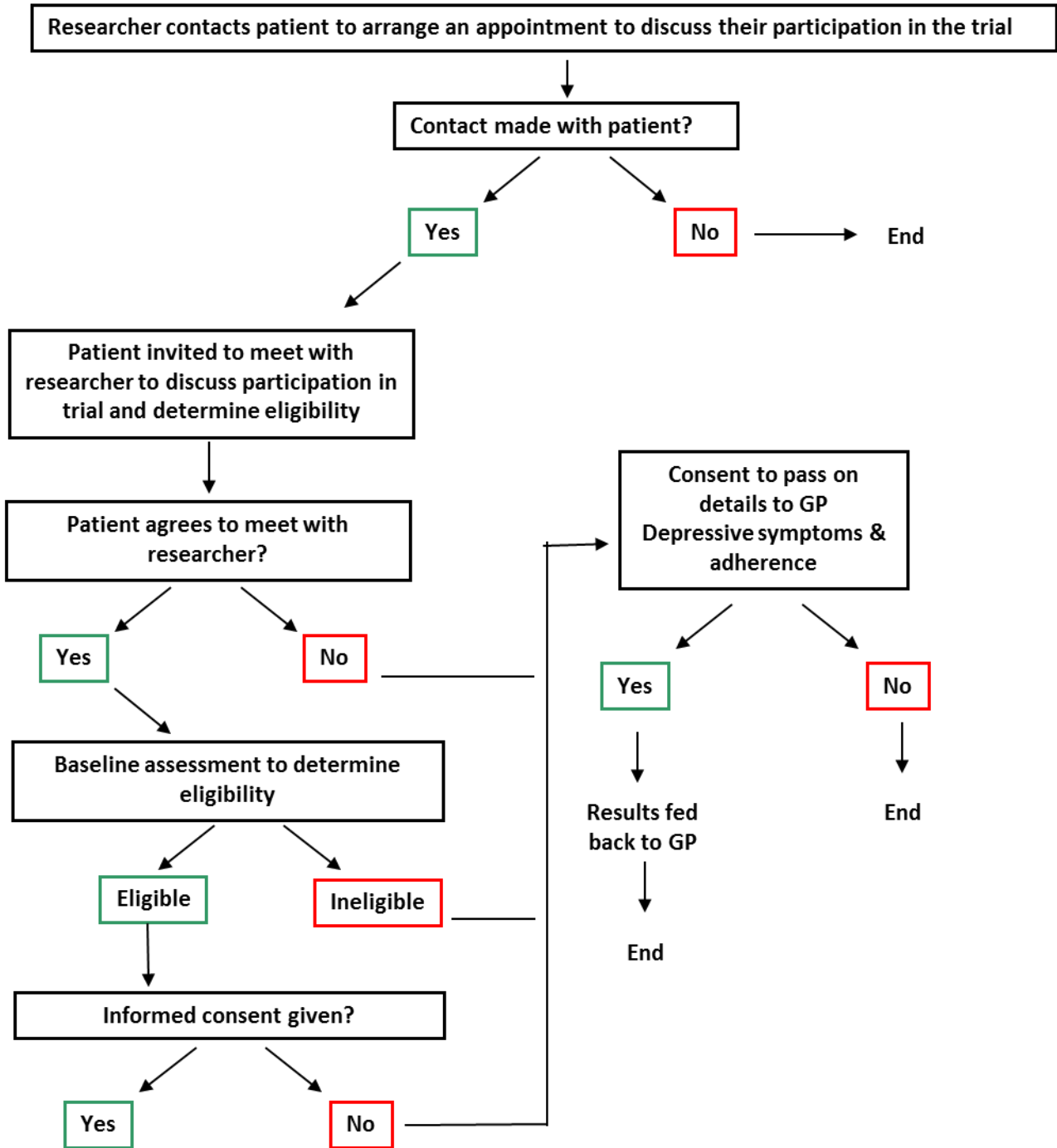
12 months

3. Trial Flow Diagram

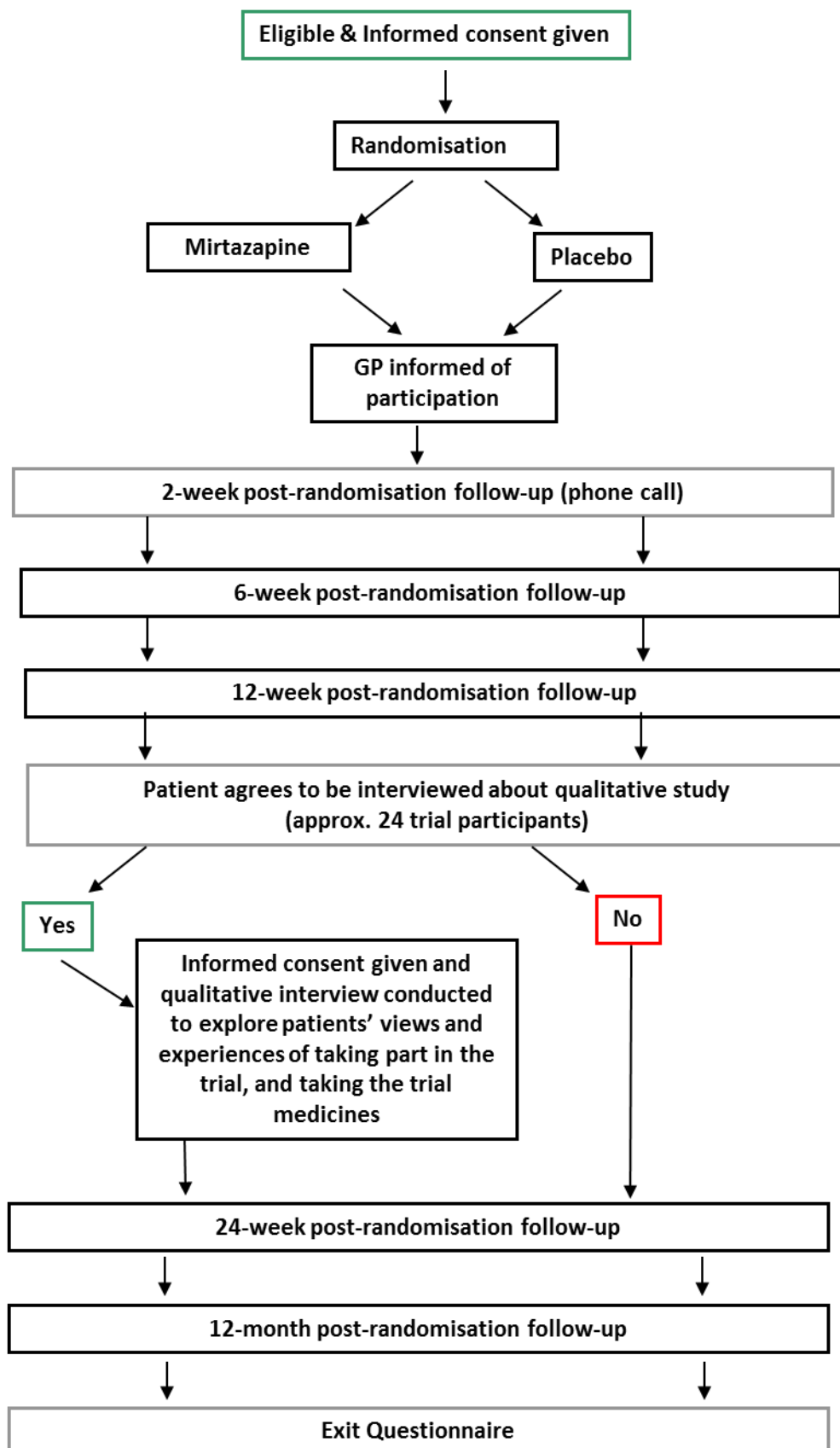
Stages 1 & 2: Identification of patients receiving repeat prescriptions of antidepressant medication and mailing of screening questionnaire



Stage 3: Appointment to discuss participation in the trial, establishing eligibility and obtaining informed consent



Stage 4: Randomisation and follow-ups



4. Timetable and Milestones

Project Timetable

Preparation: 6 months. Recruitment: 18 months. Follow-up: 12 months. Analysis & Reporting: 6 months.
Total time = 3.5 years

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Preparation																			
Recruitment																			
12 week follow-up																			
Month	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	
Recruitment																			
12 & 24 week follow-up																			
12 month follow-up																			
Month	37	38	39	40	41	42													
Analysis & Reporting																			

Milestones

Milestones for the project were initially set assuming that ethics approval, MHRA approval and research governance arrangements are in place ready for the project to commence on 3rd January 2013. As approvals were not in place until 25th July 2013, the Trial Start Date was amended to 1st April 2013, and other milestones revised accordingly.

Year 1: 1st April 2013-31st March 2014

15 Jan 2013	Trial Co-ordinator starts (Bristol)
01 April 2013	Trial Start Date
01 May 2013	Research Associates & Administrators start (all four centres)
01 Aug 2013	Recruitment begins: first patient randomised
01 Nov 2013	12 week follow-up begins
01 Feb 2014	24 week follow-up begins

Year 2: 1st April 2014 to 31st March 2015

01 Apr 2014	Recruitment continues
01 Aug 2014	12 month week follow-up begins
31 Jan 2015	Last patient randomised
01 Feb 2015	Follow-up continues for 12 months, RAs reduce to 0.5FTE

Year 3: 1st April 2015 to 31st March 2016

1 Feb 2016	Economic data collection commences
01 Mar 2016	12 month follow-ups end (incl. 1 month for reminders)
1 Mar 2016	Cleaning of follow-up data commences

Year 4: 1st April 2016 to 31st March 2017

01 May 2016	Economic data collection ends
01 Apr 2016	Analysis commences
01 Apr 2016	Report writing commences
14 Oct 2016	Drafts of final report and manuscript completed

Additional milestones including monitoring the rate of recruitment (target: 7 patients randomised per centre per month) and the 3-month follow-up rate (target: 85%).

5. Glossary of Terms

ASEC

A self-report instrument, the Antidepressant Side Effect Checklist (ASEC), which has been found to show good agreement with psychiatrists' ratings.

Baseline recruitment

A meeting with the research associate in which the research associate provides a full explanation of trial participation, takes consent, completes the trial baseline Case Report Form.

BRTC

Bristol Randomised Trials Collaboration

Centre

One of the four academic centres (Bristol, Exeter, Manchester and York), each with two PIs, from which Sites will be recruited and coordinated.

Code-break

Record held by UHBristol of allocation of active vs. placebo (and Medicine ID number) to Patient ID number.

CRF

Case Report Form. The data collection tool, where all source data is recorded.

GCP

Good Clinical Practice

IMP

Investigational Medicinal Product, also referred to as the "Trial Medicine". This is either mirtazapine or matched placebo.

Index consultation

The routine consultation between the patient and the primary care clinician responsible for the patient's routine care, in which the patient's GP identifies that the patient is suffering from depression and has had at least six weeks of treatment with an SSRI or SNRI antidepressant. The clinician introduces the trial, takes written consent for the patient to be contacted by the study team and carries out a detailed check of eligibility including checking for potential drug interactions on the GP practice information system.

Medicine ID number

The unique number assigned to the IMP at manufacture (by the IMP manufacturer using the randomisation data provided by BRTC) and assigned, to the Patient ID number according to the randomisation schedule provided to UH Bristol by the BRTC.

Medicine pack

The packaging containing the IMP uniquely identified by the Medicine ID number.

Patient ID number

The unique number that is assigned to the recruited patient by the Research Associate following informed

written consent during the baseline recruitment interview.

PIS

The Patient Information Sheet, which is given to the patient by the GP during the consultation, or posted to potential participants by the GP practice. All patients will be provided with the full PIS. A summary PIS is also sent to participants with their baseline appointment letter.

Randomisation data

A list of random numbers generated by BRTC in line with the requirements of the trial sponsor and of the medicine supplier (Sharp) and provided to Sharp (in a manner which maintains the complete blinding of the trial team) for their use in numbering the medicine packs which are provided to the four trial centres. The random numbers will form the identifiers on the open code break document sent with each delivery of medication packs.

Randomisation schedule

Instructions provided by BRTC to the four trial centres regarding active vs. placebo medicine allocation.

Responsible Clinician

The GP who takes responsibility for the clinical management of the patient, for confirming the patient's eligibility to take part in the trial and for checking for possible drug interactions on the GP practice information system.

Site

GP practice

Source data

For the MIR trial, the source data will be considered to be the data that has been recorded on the CRF by the research associate and by the patient. Where data has been entered directly online, without the use of paper forms, this will be taken as the source data.

Trial Participation Card

Trial participants will be requested to carry this with them while participating in the trial. It will record the Medicine and Patient ID numbers to be used for emergency unblinding.

Trial Prescription

If the patient is eligible to participate in the trial (following completion of the detailed eligibility check, including checking for interactions on the GP practice information system) the Local Principal Investigator will authorise a trial prescription, to be passed to the research team.

6. Lay Summary

Depression is common and most depressed patients are treated by their general practitioner (GP). Antidepressants are very widely prescribed, but a substantial proportion of those who take them do not get better. There is very little evidence to guide GPs when this happens, and most are unsure what to do when their patients do not respond to the medication. Many patients remain in a depressed state for long periods of time, despite taking antidepressant treatment.

We have recently completed a trial studying the effects of cognitive behavioural therapy for this group of patients, but we are looking for other ways to help those whose depression does not respond to initial treatment, and we think that it might be useful to use combinations of antidepressant drugs. Combination treatments are used in many areas of medicine, including other common conditions such as hypertension and diabetes.

Most of the antidepressants prescribed in the UK as first line treatment are Selective Serotonin Reuptake Inhibitors (SSRIs) like Fluoxetine (Prozac). However, there is another well-established antidepressant called

mirtazapine, that works in a different way from SSRIs and the related noradrenaline reuptake inhibitors (SNRIs). There is a strong pharmacological rationale that the distinct chemistry of mirtazapine and reuptake inhibitors act in a synergistic way.

There have been previous studies that have shown that the combination is well tolerated by depressed patients, and may be effective. We propose a large study in general practice, where most depression is treated, to examine the effectiveness and cost-effectiveness of the combination of mirtazapine and an SSRI or SNRI. We will recruit patients from general practices in four centres, Bristol, Exeter, Manchester/Keele and York. As we will be dealing with a vulnerable group of patients we will have clear policies on response to any deterioration or the emergence of risk of self-harm. We have conducted a number of studies on this patient group and continue to work closely with service-users through the local and national mental health research networks. The research team is well placed to carry out this work, as it includes psychiatrists, some of whom are expert in pharmacology, general practitioners, and statisticians who will advise on the running of the study. We have just completed a study of the same size in the same treatment resistant population and are confident we can recruit successfully to this study.

The design we want to use is a randomised clinical trial, comparing the addition of mirtazapine to a placebo for patients with depression who have had one or more trials of an antidepressant and have currently been on an SSRI or SNRI for at least 6 weeks and are still depressed. Participants who agree will be randomly allocated to receive either mirtazapine or a placebo that appears identical. Neither the patient, GP, or study investigator will know whether the patient is taking mirtazapine or placebo. They will continue to take their SSRI or SNRI antidepressant and be treated by their GP in the usual way. Participants would be free to drop out of the study at any time if they wished. All participants will be offered the option of unblinding (that is, learning whether they were taking the trial medication or a placebo) after 12 weeks, which is when the primary outcome measure of the study is taken. We will continue to follow up all participants for a year. This will allow us to see if there are medium or longer-term benefits of this combination treatment. If it proves effective, this combination has the potential to rapidly make a difference for people with depression that does not respond to usual first line antidepressant treatment.

7. Detailed Project Description

7.1 Research Objectives

First line drug treatments do not work for a substantial proportion of people with depression in primary care and general practitioners (GPs) are generally unsure what to do next. Existing randomised evidence is not very informative and we seek to address this question from the perspective of primary care (where most depression is managed). We want to investigate treatment for people with depression who have not responded to an adequate dose of a selective serotonin reuptake inhibitor (SSRI) antidepressant or an antidepressant that inhibits the reuptake of both serotonin and noradrenaline (SNRI). All patients entering the trial will be recruited from primary care and will have treatment resistant depression, defined as meeting ICD-10 (1) criteria for depression after at least 6 weeks treatment with either an SSRI or SNRI antidepressant. Our aims are: (i) to determine the effectiveness of the addition of the antidepressant mirtazapine to an SSRI or SNRI in reducing depressive symptoms and improving quality of life at 12 weeks, 24 weeks and 12 months (compared to the addition of a placebo); and (ii) to determine the cost-effectiveness of this intervention over 12 months. In addition, this study will incorporate a qualitative study to: (i) explore patients' views and experiences of taking either two antidepressant medications or an antidepressant and a placebo; (ii) identify patients' reasons for completing or not completing the study, including withdrawal from study medication; and (iii) to explore the views of general practitioners on prescribing a second antidepressant in this patient group.

7.2 Existing Research

Depression is ranked amongst the top five contributors to the global burden of disease, and by 2030 is predicted to be the leading cause of disability in high income countries (2). Antidepressants are usually the first-line treatment for depression and the number of prescriptions for antidepressants has risen dramatically in recent years. Over 40 million prescriptions were issued in the UK in 2010 (3) at a cost of

£218 million. However, the recent STAR*D study (Sequenced Treatment Alternatives to Relieve Depression) found that only one third of patients responded fully to a single antidepressant (monotherapy) and that half did not experience at least a 50% reduction in depressive symptoms following 12-14 weeks of monotherapy (4). The reasons for this non-response are complex but include what can be termed treatment resistant depression (TRD) where an adequate dose and duration of treatment has been taken. The high prevalence of treatment resistant depression means that effective interventions have the potential to substantially impact on the economic cost of this condition to the NHS, patients and society.

Defining treatment resistance

Many definitions of treatment resistance have been proposed. These definitions cover a broad spectrum ranging from failure to respond to at least 4 weeks of antidepressant medication given at an adequate dose(5) to more stringent criteria based on non-response to multiple courses of treatment(6) .

The National Institute for Clinical Excellence (NICE) now advocates that GPs should re-consider the treatment option if there has been no response after 4 to 6 weeks of antidepressant medication (7). However, there is currently little evidence to guide management irrespective of the definition. Hence we propose a more inclusive definition of treatment resistant depression (TRD); that is patients who still meet criteria for ICD-10 depression after taking an SSRI or SNRI antidepressant for a minimum of six weeks. This definition is directly relevant to UK primary care, given the uncertainty about what course of action to recommend to this group of patients.

Although this six-week criterion seems a relatively short period to define treatment resistance, many of the patients who satisfy this criterion of 'non-response,' are suffering from moderate to severe chronic depression. The baseline measures for a recent study of the effectiveness of CBT for treatment resistant depression in primary care, the COBALT study, found that 59% of those recruited had been depressed for more than 2 years; that 70% had been prescribed their current antidepressant for more than 12 months, and that 28% satisfied the ICD-10 criteria for severe depression (8 and personal communication). This data on chronicity and severity illustrates the extent of the unmet need in this population.

Existing evidence on the pharmacological management of treatment resistant depression

Current NICE guidelines (7) describe the following pharmacological strategies for sequencing treatments after inadequate response to initial treatments: switching antidepressants; augmenting medication by adding a drug which is not an antidepressant; and combining antidepressants. The guidelines comment in general on the lack of evidence and particularly that 'the evidence for the relative advantage of switching either within or between classes is weak.' Connolly et al comment that switching antidepressants after inadequate response is not 'unequivocally supported by the data, although switching from an SSRI to venlafaxine or mirtazapine may...offer greater benefits' (6).

The evidence for the effectiveness of augmentation with a non-antidepressant is likewise of variable quality. There is some evidence for augmentation with lithium or thyroid hormone, but mainly in combination with tricyclic antidepressants, which are prescribed much less often today. The use of the atypical antipsychotics quetiapine and aripiprazole to augment the newer antidepressants is better supported. There is very little evidence on combining two antidepressants; this is discussed in more detail below. This summary largely echoes the recently revised guidelines of the British Association for Psychopharmacology (9). We are currently carrying out a systematic review, and although it is not yet finished, we are confident that we have identified the important literature on this topic.

Despite some evidence for its effectiveness, augmentation of SSRIs with atypical antipsychotics has not been adopted with any enthusiasm in primary care. Perhaps this is because of concerns about the potential toxicity of these drugs, and perhaps because they are usually initiated in secondary care. GPs are also aware of their propensity to cause morbid obesity amongst patients with schizophrenia and the future epidemic of metabolic disorders that is expected. In fact current NICE guidance is that antidepressants should not be combined or augmented without the advice of a consultant psychiatrist (7).

It is more likely that general practitioners would consider adding a second antidepressant as part of the management of TRD. They are more familiar with the drugs and their starting routines. There is less concern about the adverse effects of antidepressants than lithium and antipsychotics, and in the case of lithium, less need for regular blood testing. In general, stepwise combination of drug treatments is a standard part of the management of chronic diseases in primary care such as asthma and hypertension and has led to improved clinical outcomes. GPs are comfortable with this model of care and would probably readily adopt this strategy if it were found to be effective. We think there may be an opportunity to substantially improve the treatment of depression in primary care by using antidepressants in combination. However, one of the reasons that this strategy has not been adopted is the lack of convincing evidence for its effectiveness, especially in the primary care setting.

There is a rationale for adding a second antidepressant to SSRIs or SNRIs with a different and complementary mode of action. Mirtazapine, a presynaptic α_2 -adrenoreceptor antagonist, increases central noradrenergic and serotonergic neurotransmission. Its mechanism of action is different to that of both SSRIs and SNRIs. Mirtazapine acts by inhibiting the negative feedback from 5-hydroxytryptamine and noradrenaline (NA) that has already been released by the neurone; SSRIs and SNRIs inhibit reuptake of 5HT and NA from the synaptic cleft. Thus treatment with mirtazapine in combination with either an SSRI or SNRI may produce a sustained increase in both 5-HT and NA synaptic availability. There is the potential for a synergistic action and this could enhance clinical response compared to those patients receiving only an SSRI or SNRI. Mirtazapine is now off patent and relatively inexpensive.

Because of its different mechanism of action there is an argument that switching to mirtazapine alone after SSRI treatment failure might be an effective strategy, rather than subjecting patients to the potential adverse effect burden of a second medication. The STAR*D study compared mirtazapine to nortriptyline in a group of patients who had not responded to two consecutive antidepressant monotherapy regimes. The rates of remission were low for both drugs (10), suggesting that switching to mirtazapine is not the most useful strategy.

In spite of the potential benefit for combining mirtazapine with an SSRI there is relatively little trial evidence supporting this strategy. Carpenter et al compared the addition of mirtazapine to an SSRI with placebo in a group of 26 patients who had not responded to at least 4 weeks of monotherapy. Although the sample size is very small, the results in terms of effectiveness and tolerability are encouraging (11) but more definitive evidence is required before widespread adoption. In patients who have not failed previous treatment Blier et al reported that mirtazapine in combination with an SSRI gave a greater improvement than monotherapy (12), and that it was well tolerated with both an SSRI and an SNRI (venlafaxine) (13). In contrast a larger study found no benefit from combining antidepressants, including mirtazapine and venlafaxine, over SSRI monotherapy with escitalopram (14) but had a higher side-effect burden.

It is therefore important to undertake a study to investigate the effectiveness of the addition of mirtazapine to SSRIs or SNRIs in primary care. In the UK most depression is diagnosed and treated in primary care, and this is where most antidepressants are prescribed, and most treatment resistance encountered. Any such trial should be pragmatic in having a definition of treatment resistance that reflects the experience in primary care, and offering a treatment that can be relatively easily adopted by GPs if it proves effective. The rise in antidepressant prescribing has continued at a steady rate in the UK despite the introduction of the government's initiative to increase access to psychological services (IAPT). Failure to adequately respond to treatment is a substantial problem and there is a need to develop the evidence base for the rational prescribing of antidepressants in primary care.

We considered in the trial design whether combining antidepressants should be compared with switching to a different antidepressant, as this is often the choice faced by GPs in practice. We decided against including a switching arm in the protocol because this would require an additional treatment arm which is practically unfeasible both in terms of size of study required, and because the large STAR*D study found

that few patients agreed to be randomised between switching and combination arms (15). Patients who agreed to switch antidepressant had frequently discontinued the previous treatment and those agreeing to combination treatment had gained some, although insufficient, benefit and were reluctant to switch from their current treatment (16). In this study we shall investigate whether the addition of mirtazapine provides added and sustained benefit over persisting with current treatment.

Ongoing studies

A search of the international databases for the registration of randomised controlled trials has not found any recent or current trials of mirtazapine for TRD. A trial of Mirtazapine for patients who have not responded to two weeks of treatment with Paroxetine (an SSRI) is planned, based at Capital medical University, Beijing (NCT01458626). The study population is different in that it is made up of patients with a new episode of depression who have not responded quickly to an SSRI, rather than subjects with a treatment resistant illness.

Rapidly making a difference to clinical decision making within the NHS

There is substantial unmet clinical need in this population. The intervention is simple, and is likely to be taken up in primary care if found to be effective. The evidence from the trial will make a contribution to rational and effective prescribing in this important area. We think there may be a real opportunity to substantially improve the treatment of depression by combining antidepressants with complementary actions. This strategy is only rarely used in primary care at present.

Summary

Antidepressants are the treatment of choice in primary care for depression, but treatment resistance is common. The current lack of evidence means that clinicians are increasingly faced with a dilemma as to what action to recommend to patients who do not respond to a course of treatment with antidepressants. There are a number of pharmacological strategies for improving response but the evidence base is small. There are good reasons to suppose that mirtazapine, an antidepressant with a complementary mechanism of action to the SSRIs and SNRIs, might act in combination with either to improve outcome. There is preliminary evidence from small studies to suggest that this is the case. We propose a large pragmatic placebo controlled trial of the combination of mirtazapine with an SSRI or SNRI in depressed patients who have not responded to at least 6 weeks treatment with an SSRI or SNRI, to test this hypothesis. Given the high prevalence of depression in primary care, an effective intervention has the potential to have a substantial impact on the health and economic burden associated with this patient group.

8 Trial Objectives and Design

8.1 Trial objectives

To examine the effectiveness of the addition of the antidepressant mirtazapine for patients in primary care who are depressed despite treatment with an Selective Serotonin Reuptake Inhibitor (SSRI) or Serotonin and Noradrenaline Reuptake Inhibitor (SNRI) antidepressant. Outcomes will be measured at 12 and 24 weeks and at 12 months, to establish whether there are both short and longer term benefits of treatment. Cost effectiveness will be assessed at 12 months. A nested qualitative study will explore patients' and general practitioners' (GP) views of the use of an additional antidepressant.

8.2 Study Design

This is a two parallel group multi-centre pragmatic placebo controlled randomised trial with allocation at the level of the individual. The primary outcome will be at 12 weeks. The double-blinded randomised allocation will be maintained for a period of 12 months, although participants can be unblinded at their request or the request of their GP after the primary outcome at 12 weeks, and outcomes will be measured at 24 weeks and 12 months. These include cost-effectiveness which will be assessed at 12 months.

8.3 Study Site

The study will be based in primary care in four sites, Bristol, Exeter, Hull/York and Manchester/Keele. The Chief Investigator and Trial Manager will be based in Bristol and the study will be coordinated from Bristol.

8.4 Primary research questions

To investigate in adults of 18 years and over in primary care with treatment resistant depression (TRD) if the use of mirtazapine, compared with placebo, reduces the symptoms of depression measured as a continuous variable at 12 weeks using the Beck Depression Inventory (BDI) (17).

We will also describe a binary variable using the BDI, representing response, defined as a reduction in depressive symptoms of at least 50% compared to baseline, a widely used definition of improvement

8.5 Secondary research questions

In relation to the use of mirtazapine compared with placebo we will also:

1. Investigate the rate of remission of symptoms, defined as a score on the BDI of less than 10
2. Investigate any change on a measure of generalized anxiety, the Generalised Anxiety Disorder & Questionnaire (GAD-7) (18)
3. Measure all of the above outcomes at 24 weeks and 12 months
4. Measure antidepressant use and adherence
5. Estimate the cost-effectiveness from the perspectives of the NHS, patients, and society
6. Compare all adverse events including: any new symptoms or worsening of existing symptoms, consultations for a documented deterioration in illness and Serious Adverse Events

8.6 Population

Adults over 18 in primary care with depression who have not responded to at least six weeks of treatment with an SSRI or SNRI antidepressant

8.7 Intervention and Placebo

Participants will be randomly assigned to one of two treatments (i) one x 15mg encapsulated mirtazapine daily for 2 weeks followed by two x 15mg encapsulated mirtazapine for up to 50 weeks or (ii) identical placebo. Participants are free to withdraw from the study at any time. Patients, clinicians, outcome assessors and the research team will be blinded to allocation. Clinicians will not be restricted in their use of psychological services.

8.8 Outcomes

Primary outcomes:

1. Change in BDI score at 12 weeks compared with baseline, measured as continuous variable
2. Rate of response, measured as an improvement of at least 50% in BDI score at 12 weeks compared with baseline

Secondary outcomes:

1. The rate of remission of symptoms, defined as a score on the BDI of less than 10 at 12 weeks
2. Change on a measure of generalized anxiety, the Generalised Anxiety Disorder & Questionnaire (GAD-7) at 12 weeks
3. Measure all of the above outcomes at 24 weeks and 12 months
4. Measure antidepressant use and adherence
5. Quality of life using the EQ-5D-5L (19)
6. Estimate the cost-effectiveness from the perspectives of the NHS, patients, and society
7. Compare all adverse events including: any new symptoms or worsening of existing symptoms, consultations for a documented deterioration in illness and Serious Adverse Events

8.9 Expected duration of the trial

The overall trial duration is 42 months. The trial commenced on 1st April 2013, with recruitment of patients beginning in August 2013. We anticipate that the period of recruitment will be 18 months. Participants will be invited to stay in the study for 12 months. The primary outcome is at 12 weeks, and we

anticipate substantial attrition after this time. Nonetheless we will endeavour to follow up all participants for 12 months to look for longer-term outcomes in this chronic illness.

9 Selection and withdrawal of participants

9.1 Inclusion criteria (all must apply)

- Adults (over 18 years) in primary care
- Depression treated with at least 6 weeks at recommended BNF doses of any of the following SSRI or SNRI antidepressants: fluoxetine, sertraline, citalopram, escitalopram, fluvoxamine, paroxetine, duloxetine, or venlafaxine
- Have adhered to their medication (Adherence to medication is difficult to measure. In order to operationalize our definition of treatment resistance, we will use the Morisky 4-item self-report measure of compliance (20) as adapted for the COBALT trial. The Morisky measure has previously been validated against electronic monitoring bottles, with a score of zero (range: 0 – 4) indicating at least 80% compliance (21). Given the relatively long half-life of antidepressant medication, individuals who have forgotten to take one or two tablets will not be excluded.)
- Scoring at least 14 on the BDI
- An ICD-10 diagnosis of depression (assessed using the Computerised Interview Schedule – Revised version (CIS-R) (22)

9.2 Exclusion criteria (presence of any warrants exclusion)

- Currently taking combined or augmented antidepressant treatment
- Currently having their medication managed by a Psychiatrist
- Bipolar disorder
- Psychosis
- Alcohol/substance abuse/dependence
- Pregnancy, planning pregnancy, breast feeding
- Patients who are unable to complete the study questionnaires
- Past history of an adverse reaction to mirtazapine
- Current treatment with a mono-amine oxidase inhibitor including moclobemide
- Other medical contraindications to mirtazapine
- Dementia (formal diagnosis)

9.3 Recruitment of participants

The trial aims to recruit participants from primary care with depression that has not responded to at least 6 weeks treatment with SSRI or SNRI antidepressants. We plan to recruit 470 patients over 18 months from 96 practices in 4 centres, a target of 7 patients randomised per month. We will use two methods of recruitment: record search and in-consultation recruitment.

Method 1: record search

GP practices will conduct a search of their computerised records for potentially eligible patients (defined as those who have been prescribed SSRI or SNRI antidepressants for at least 6 weeks at an adequate dose (Appendix 7), as recommended in the British National Formulary (BNF; www.bnf.org.uk/bnf/)). These patients will then be mailed an invitation by their GP to participate asking for their permission to be contacted by the research team. Patients who have not responded after two weeks will be sent one reminder letter by the practice.

Those potential participants agreeing to contact would be mailed a brief questionnaire asking about their depressive symptoms and use of medication (to identify those who might have TRD). Potential participants would be invited to an appointment with a researcher to explain the trial, perform the baseline assessment, establish eligibility and obtain written informed consent.

Method 2: in consultation

GPs can identify patients in consultation that they think might be suitable for the trial. They will introduce the trial and ask the patient for their consent to be contacted by the research team. Those potential participants agreeing to contact would be mailed a brief questionnaire asking about their depressive symptoms and use of medication (to identify those who might have TRD). Potential participants would be invited to an appointment with a researcher to explain the trial, perform the baseline assessment, establish eligibility and obtain written informed consent.

9.4 Selection of sites

Recruitment will take place in general practices that will be part of the Primary Care Research Network for England (PCRN-E). All four centres will build upon well-established local research networks and have a strong record of research in primary care and experience of, and commitment to, mental health trials. The University of Bristol will follow its Green Light (monitoring) Process, in line with MHRA requirements, in order for the trial sponsor / monitor to document the preparedness of the other collaborating centres (Exeter, Manchester/Keele and Hull/York) to conduct recruitment locally. Following training from, and with the support of, their local centres, these sites will recruit autonomously using methods similar to those successfully employed in previous studies (COBALT, IPCRESS, GENPOD). The randomisation system (BRTC) will mean no geographical restriction to site participation other than local research governance approval, and sites will be reimbursed for the cost of recruiting and conducting notes reviews through NHS Service Support Costs.

We will seek adoption by the Mental Health Research Network (MHRN) and the Primary Care Research Network (PCRN). All the participating centres are part of their local MHRN/PCRN research hubs, which would provide support with recruitment.

9.5 Training for the recruiting sites

Each GP practice recruiting to the trial will receive information and advice on all trial recruitment procedures prior to the start of recruitment. This will be provided to Bristol centre sites by the Trial Manager, with the assistance of other members of the trial team as appropriate. A training log will be maintained within the Trial Master File. Guidance will be provided to Exeter, Manchester/Keele and York/Hull centre sites by the local trial team with assistance from the Bristol trial centre as required.

9.6 Randomisation procedure and Code Break

Randomisation will be stratified by centre ($n = 4$), with minimisation used to ensure balance in baseline BDI score (using approximate tertiles derived from the COBALT baseline scores; <26 ; $26-34$, ≥ 35), gender and whether the patient is currently receiving a psychological therapy. We will use minimisation with a probability weighting of 0.8 in order to reduce predictability (23). After an eligible patient has consented to participate, their details will be entered onto a secure, web-based data collection platform along with the Patient ID number and a Medicine ID number will be allocated to them.

The UH Bristol pharmacy will hold the randomisation schedule and a log of which Medicine Pack was allocated to each patient (hereafter referred to as the Code-break) and provide a 24 hour emergency unblinding service. During working hours (Monday to Friday, 9am to 5pm), concerned clinicians should contact the UH Bristol pharmacy clinical trials unit on 0117 342 4175. Out-of-hours the Trust on-call Emergency Duty Pharmacist is available via the Trust switchboard 0117 923 0000. Each participant will be given a Trial Participation Card with details of who their Responsible Clinician should contact in the event of an emergency. The Trial Manager and Centre Co-ordinators will also hold these cards.

A standardised procedure for breaking the code will be available (UH Bristol Emergency Code Break Procedure (version CT 5 02)). When necessary, the code for a particular participant can be broken at any moment during the trial. Before the 12 week primary outcome, the codes will only be broken in case of a medical emergency, if unblinding will influence the patient's treatment, or the patient has suffered an unexpected serious adverse event (e.g. anaphylaxis; admission to hospital with life threatening illness). After the 12 week primary outcome, the code can be broken at the request of the participant or their GP.

The Code-break will only be released to the investigative team once written confirmation has been received that primary outcome data analysis is complete. The UH Bristol Pharmacy will also record a list of all participants and their treatment allocation and file this in the pharmacy trial file and provide a copy to the Trial Manager at the end of the trial. Formal SOPs will be developed to describe each of these procedures in detail.

9.7 Other reasons for withdrawal from the trial medication

During the study period the GP or other health care professional may decide to make changes to the participant's psychotropic drug regime, for example because of failure to respond. All participants will be taking an SSRI or SNRI antidepressant at entry to the study. If it is decided that it is advisable to change from one SSRI to another, or to swap an SSRI to an SNRI or vice versa, then there is no reason for the participant to withdraw from the trial medication. However, if the decision is to commence a mono-amine oxidase inhibitor (MAOI) then the participant should be withdrawn from the trial medication for two weeks before this is done. If the participant's GP or another health professional decides that it is appropriate for the participant to commence another augmenting treatment, such as Lithium or an antipsychotic drug, then we would advise that they be withdrawn from the trial medication. We will include this advice on the appropriate information sheets.

We anticipate that a proportion of participants who request unblinding at 12 weeks will have benefitted from the addition of mirtazapine to their treatment and will wish to continue this treatment. Likewise, some of those who have been in the placebo arm of the study, when unblinded, may wish to try treatment with mirtazapine. Further prescribing of trial medication will not be available once participants are unblinded and would be at the discretion of the GP. We will continue to prescribe trial medications for those who decide to remain blinded.

Participants are of course free to withdraw from the trial medication at any time. We will offer to continue to follow up those who withdraw from the trial medication as part of our intention to treat analysis.

10 Trial Procedures

10.1 Postal Screening

Patients who have agreed to be contacted by either method of recruitment will be sent a postal screening questionnaire. This will contain a Beck Depression Inventory (BDI), a measure of adherence to medication (Morisky), a question about duration of medicine use, a series of simple demographic questions, and a list of the main exclusion criteria. All those who respond positively to the screening questions will be invited to a baseline assessment with a research associate, either in their own home or at their general practice. We will ask the GPs to provide anonymised data on the age and gender of those patients who were mailed an invitation to participate but who did not respond in order to assess the generalisability of our findings. The GPs will be asked to review all those who are invited to the baseline assessment and sign a form to confirm that they are suitable to be prescribed mirtazapine.

10.2 Baseline assessment

The baseline assessment will be conducted by a research associate. It will take place in the patient's home or at their GP's surgery. The research associate will explain the study in detail. If the potential participant is agreeable they will complete the following questionnaires:

- The Beck depression inventory (BDI)
- The General Anxiety disorder questionnaire
- The Morisky (adherence to medication)
- The Patient Health Questionnaire version 9 (PHQ9) a brief measure of depression
- The EQ-5D-5L a brief measure of health related quality of life

- The SF-12 a brief measure of social function
- The Clinical Interview Schedule (revised) an in-depth psychiatric questionnaire which gives an ICD-10 diagnosis.
- The ASEC measure of antidepressant side effects

Participants will be asked for details of their prescribed medication, prior use of antidepressants and whether they have ever seen a psychiatrist. We will also ask them about the strength of their preference for active treatment over placebo (as this may potentially affect medication adherence and outcomes). Additional information will be collected on life events, social support and use of alcohol (24). In addition, socio-demographic details will be recorded (age, gender, ethnicity, marital status), together with information on a number of socio-economic markers (employment status, housing situation, financial stress).

Potential participants who score more than 14 on the BDI, have been adherent to antidepressants for at least 6 weeks (using the Morisky) and who have an ICD-10 diagnosis of depression using the CISR, will be invited to enter the trial. If they agree they will be formally consented by the research associate. If the patient is deemed to be eligible the RA will confirm this with the local PI. Following the baseline assessment eligible participants will be randomised using the automated randomisation service provided by BRTC. Randomisation will be by means of a computer-generated code. Use of an automated telephone randomisation system will ensure concealment of allocation. Randomisation will be stratified by centre. Once this has been done the United Hospitals Bristol (UHB) pharmacy, which is the central trial pharmacy, will be notified. A patient pack containing an initial 8 week supply of medication will be sent by registered post from UHB pharmacy either to the participant's GP surgery or in exceptional circumstances, their home.

It is our experience from a number of studies using the same or a similar battery of tests that the baseline interview lasts between 75 and 90 minutes.

10.3 Follow-up/subsequent assessments

2 weeks: at 2 weeks post baseline we will contact participants briefly by telephone. The purpose of this contact is to check participants have received and started their trial medication. Participants will be advised that this is the time point at which they should increase their dose to two capsules.

6 weeks: at 6 weeks the research associate will contact the participant and ask again about adherence, adverse events, and ask participants to complete the BDI. If participants wish to continue with the trial medication the research associate will notify the UHB pharmacy and a further 6 weeks supply will be sent out at this time. This will be done 2 weeks in advance of the initial supply running out to ensure continuity of supply.

12 weeks: This is the point at which the primary outcome is measured. In addition to the BDI (the study's primary outcome measure), participants will also be asked to complete the Morisky, the ASEC, the PHQ9 (26), the GAD7, the EQ5D5L, the SF-12, and a health economics questionnaire.

After the 12-week follow up, participants may request non-emergency unblinding, and this request will be forwarded to the Bristol Trial team. For those participants who wish to continue receiving the blinded trial medication, the research associate will inform the UHB pharmacy who will send a further 6-week supply. Further deliveries up to the end of the study at 52 weeks will be arranged by telephone between the participant and the research associate.

24 weeks: as for 12 weeks, (but without the ASEC measure)

12 months: this is the end of the trial medication period. The questionnaires are the same as 12 weeks. In addition, participants will be asked to complete a short feedback questionnaire after their 12 month follow-up.

Throughout the follow-up process we will be sure to ask in detail about possible adverse effects and to advise participants to consult their GP about these if appropriate. Although there are a number of questionnaires, they are all brief, apart from the CISR, which is only administered once, at baseline. These questionnaires have been found to be acceptable to participants in a number of our previous studies. Participants will be sent a goodwill gesture of £5 with the 12-week, 24 week, and 12-month questionnaires.

A full schedule of questionnaires is attached as appendix 5.

10.4 Withdrawal of trial participants

Participants have the right to withdraw from the trial at any time for any reason, without their medical care being affected. Where possible, data already collected will continue to be used in the trial and patients who withdraw from the trial will be asked if they are still willing to provide follow-up data. If a patient withdraws, the reason for and type of withdrawal will be documented in the CRF.

Principal Investigators also have the right to withdraw patients from the trial drug in the event of inter-current illness, Adverse Events (AEs), Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), protocol violations, administrative reasons or other reasons. The reason for withdrawal will be documented in the CRF. If the participant is withdrawn due to a serious adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised. It is understood by all concerned that an excessive rate of withdrawal can render the trial uninterpretable, therefore unnecessary withdrawal of patients will be avoided.

Although there is no evidence that the medication is teratogenic, if a patient discovers that she is pregnant during the trial, she will be instructed to stop her trial medications immediately, though she will be able to continue to participate in completion of the trial outcome measures if she wishes. A longer monitoring period will be put in place to establish the safe delivery of a healthy infant, at which point follow-up will stop.

We will collect the trial Medicine Packs from patients who withdraw. Recruitment will continue until the sample size is reached

A formal SOP will be developed to describe the withdrawal process.

11. Trial Medication

11.1 The Investigational Medicinal Product and comparator

The Investigational Medical Product (IMP) for this trial will be Mirtazapine: 1 x 15mg oral capsule per day for 2 weeks followed by 2 x 15mg oral capsule per day for up to 12 months. The IMP will be encapsulated and the placebo will be an identical capsule filled with an inert excipient. The placebo capsule will exactly match the encapsulated IMP in dimensions and appearance, such that allocation concealment and blinding of the trial is maintained. The IMP will be encapsulated and the placebo manufactured by Sharp Clinical Services.

11.2 Packaging, labeling and dispensing

The labelling of medication packs will be MHRA approved and conform to Annexe 13 (GMP) and Article 13.3 of Directive 2001/20/EC. Each Medication Pack will have a Medicine ID number, randomly generated to ensure mirtazapine and placebo medicine packs are indistinguishable (e.g. avoid all placebo packs being assigned an odd number) and thus maintain allocation concealment. This random number will be generated by the Bristol Randomised Trials Collaboration and provided to the manufacturer who will use it to form the identifier and include it with the open code break document sent with each delivery of medication packs to the centres.

Sharp Clinical Services will provide QP services and distribution and project management. They will ship labelled and numbered packages to UHB Clinical Trials Pharmacy, where the trial medication will be stored under controlled conditions. Storage will be secure, and there will be a delegation log for access, for which the UHB trial pharmacy will take responsibility. UHB pharmacy will dispense individual patient packs and oversee the packaging and posting of those packs. Patient packs containing no more than 2 months supply

of the trial medication will be posted by recorded delivery to the participant's GP surgery, or, in exceptional circumstances, their homes. All deliveries will be logged to ensure drug accountability. The trial medication will be shipped and stored in conditions in line with manufacturer's stability data.

11.3 Dosing regimen

According to the randomisation schedule a participant will receive either mirtazapine or placebo. The allocation will be unknown to the clinician and participant. Regardless of allocation each participant will be asked to take one capsule a day for the first two weeks and two capsules daily thereafter.

11.4 Drug Accountability

Activity	Responsibility
QP release of medicine	Sharp Clinical Services
Labelling and Packaging	Sharp
Release of medication to UHB pharmacy	Sharp
UHB Pharmacy receives, stores and prepares patient packs	UHB pharmacy
UHB Pharmacy posts patient packs to individual participants. Pharmacy maintains dispensing log	UHB Pharmacy
Collection of unused medication and return to UHB pharmacy for IMP accountability check	RAs in trial centres UHB Pharmacy

11.5 Participant adherence

Participants will be asked about adherence at all the follow-up points and will complete the Morisky measure of adherence if appropriate. It will be requested that unused medicines are returned to the research associates for safe disposal.

11.6 Concomitant Medication

Pharmacodynamic interactions:

Mirtazapine should not be administered concomitantly with Monoamine Oxidase (MAO) inhibitors or within two weeks after discontinuation of MAO inhibitor therapy. Likewise about two weeks should pass before patients treated with mirtazapine should be treated with MAO inhibitors. Participants in this study will not be treated with MAO inhibitors and GPs will be advised to wait at least 2 weeks after stopping the trial medication before starting an MAO inhibitor.

Co-administration with other serotonergic active substances (Ltryptophan, triptans, tramadol, linezolid, lithium and St. John's Wort – Hypericum perforatum – preparations) may lead to an incidence of serotonin associated effects and participants will be advised not to take any of these medications.

Mirtazapine may increase the sedating properties of benzodiazepines and other sedatives (notably most antipsychotics, antihistamine H1 antagonists, opioids). Caution should be exercised when these medicinal products are prescribed together with mirtazapine.

Mirtazapine may increase the CNS depressant effect of alcohol. Participants will therefore be advised to be cautious in their intake of alcohol while taking mirtazapine.

11.7 Known adverse effects

Please refer to the Summary of Medicinal Product Characteristics (attached) and the British National Formulary

11.8 Stopping the trial medication

All participants will be advised to discuss stopping trial medication with their GPs. We will inform participants that should they wish to stop the trial medication, they should reduce to one capsule daily for two weeks before stopping their medication. This is to reduce the possibility of a withdrawal syndrome (27).

11.9 Return and destruction of medicines

Any medicine that is returned will be passed to UH Bristol for destruction in line with the UH Bristol pharmacy medication disposal SOP.

12 Assessment of effectiveness

Primary outcomes:

1. Change in depression symptoms measured as a continuous variable using the BDI at 12 weeks
2. Response in depression symptoms, a binary variable defined as a reduction of at least 50%

Secondary outcomes:

3. Remission of depression symptoms (a score of less than 10 using the BDI)
4. Change in anxiety symptoms as measured using the GAD-7 at 12 and 24 weeks and 12 months
5. Adverse events (see above) including reconsultation for a documented deterioration in illness or hospital admission (symptom diary, telephone call at 2, 6 and 12 weeks and primary care notes review). We will also include a standard measurement of adverse effects at three months and 12 months, a self-report instrument, the Antidepressant Side Effect Checklist (ASEC)
6. Quality of life using the EQ-5D-5L (as recommended by NICE, paper based questionnaire administered at 12 and 24 weeks and 12 months)
7. Number of primary care consultations, by type e.g. face-to-face, telephone, etc. and who seen; and prescribed medication from practice records
8. A questionnaire, administered at 12 and 24 weeks and 12 months, will provide information on: use of other primary and community care services (NHS Direct, attendances at walk-in centres, use of community health care services); secondary care related to mental health (number of out-patient visits, type of clinic, and reason for visit; inpatient stays, length of stay and reason); use of social services and disability payments received; personal costs related to mental health (expenditure on over-the-counter medication, expenditure on prescriptions, travel costs associated with health care visits, loss of earnings, out of pocket expenditure on other services e.g. private counselling or complementary and alternative therapies, child care and domestic help); time off work and unpaid activities
9. Adherence to antidepressant medication, measured using a standardised instrument (Morisky).

13 Assessment of safety

13.1 Definitions

13.1.1 Adverse Event (AE)

AEs are defined as any untoward medical occurrence in a clinical trial participant. An AE does not necessarily have to have a causal relationship with the trial treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (International Conference on Harmonisation [ICH] definition). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. All AEs will be recorded

in the Case Report Form (CRF) for the duration of the participant's direct involvement in the trial (12 months).

13.1.2 Serious Adverse Event (SAE)

A SAE is defined by ICH as any untoward medical occurrence that at any dose of the trial medication meets any of the following conditions:

1. Results in the death of the participant

2. Is life-threatening

The term "life-threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

3. Requires inpatient hospitalisation or prolongation of existing hospitalisation

For any event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of these outcomes, the CI should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to UH Bristol (who acts on behalf of the Sponsor in these instances).

4. Results in persistent or significant disability / incapacity

Any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.

5. Is a congenital anomaly / birth defect

Exposure to the trial drug before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child.

6. Other medical events

Medical events that may jeopardise the subject or may require an intervention to prevent a characteristic or consequence of a SAE. Such events are referred to as 'important medical events' and are also considered as 'serious' in accordance with the definition of a SAE.

13.1.3 Adverse Event Associated With the Use of the Drug

An AE is considered to be associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed below:

- **Not related:** An AE that is not related to the use of the drug.
- **Doubtful:** An AE for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.
- **Possible:** An AE that might be due to the use of the drug and for which an alternative explanation, e.g. concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable and therefore, the causal relationship cannot be excluded.
- **Probable:** An AE that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by IMP withdrawal). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).
- **Very likely:** An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by IMP withdrawal and re-introduction).

13.2. Procedure for reporting

All adverse event reporting will be in accordance with the MIR Standard Operating Procedure for Adverse Event Reporting (Appendix 3).

13.2.1 All Adverse Events

All AEs will be reported by the Chief Investigator from the time a signed and dated informed consent form is obtained until completion of the last trial-related procedure (collection of follow-up data 12 months after randomisation). Those occurrences meeting the definition of SAEs must be reported using the Serious Adverse Event Form (see Appendix 3), including SAEs spontaneously reported to the Investigator within 30 days after the participant has completed the trial (including post trial follow-up, as above). UH Bristol, on behalf of the Sponsor, will evaluate any safety information that is spontaneously reported by a CI beyond the time frame specified in the protocol. All AEs, regardless of seriousness, severity, or presumed relationship to trial drug, must be recorded in the source document and the CRF, together with any measures taken. All Centre PIs must record in the CRF their opinion concerning the relationship of the adverse event to trial therapy. UH Bristol, on behalf of the Sponsor, assumes responsibility for appropriate reporting of adverse events to the regulatory authorities.

13.2.2 Serious Adverse Events (SAEs)

All SAEs must be reported to the UH Bristol contact (0117 342 0233) and Centre PI by a delegated member of the research team within 24 hours of their knowledge of the event. The Chief Investigator and Sponsor should also be informed. All SAEs that have not resolved by the end of the trial (i.e. by the end of the primary care notes review follow-up period), or that have not resolved upon discontinuation of the participant's participation in the trial, must be followed until any of the following occurs:

- the event resolves
- the event stabilises
- the event returns to baseline, if a baseline value is available
- the event can be attributed to agents other than the trial drug or to factors unrelated to trial conduct
- when it becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The death of a participant is considered an SAE, as is any event requiring hospitalisation (or prolongation of hospitalisation) that occurs during the course of a participant's participation. Exceptions to this are hospitalisations for:

- social reasons in absence of an adverse event
- in-clinic protocol measures
- surgery or procedure planned before entry into the trial (must be documented in the CRF)

13.2.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

All relevant information about a SUSAR which occurs during the course of the trial and is fatal or life-threatening will be reported within 7 days to the MHRA and the relevant ethics committee by UH Bristol, on behalf of the Sponsor. The expectedness of an adverse event will be determined by whether or not it is listed in the Summary of Product Characteristics, the British National Formulary and study protocol. All relevant information about a non-fatal or life-threatening SUSAR which occurs during the course of the study will be reported within 15 days to the MHRA and the relevant ethics committee by UH Bristol, on behalf of the Sponsor. The expectedness of an adverse event will be determined by whether or not it is listed in the Summary of Product Characteristics, the British National Formulary and study protocol.

13.3 Expected Adverse Events and Reactions

Adverse reactions of mirtazapine as listed in the Summary of Medicinal Product Characteristics (February 2015)

System	Very common >1/10	Common 1/100 – 1/10	Uncommon 1/1000-1/100	Rare 1/10,000- 1/1000	Frequency not known ⁷
Metabolism and nutrition disorders	Increase in appetite ¹ Weight increased ¹				Hypnoatraemia
Gastrointestinal disorders	Dry Mouth	Nausea ³ Diarrhoea ² Vomiting ² Constipation ¹	Oral Hypoaesthesia	Pancreatitis	Mouth oedema Increased salivation
Nervous system	Somnolence ^{1,4} Sedation ^{1,4} Headache ²	Lethargy ¹ Dizziness Tremor	Paraesthesiae ² Restless Legs Syncope	Myoclonus	Convulsions Serotonin Syndrome Oral paraesthesia Dysarthria
Psychiatric disorders		Abnormal dreams Confusion Anxiety ^{2,5} Insomnia ^{3,5}	Nightmares ² Mania Agitation ² Hallucinations Psychomotor restlessness (incl. akathisia, hyperkinesia)	Aggression	Suicidal ideation ⁶ Suicidal behaviour ⁶
Musculo-skeletal system		Back pain ¹ Arthralgia Myalgia			Rhabdomyolysis
Vascular disorders		Orthostatic hypotension	Hypotension ²		
Blood and Lymphatics					Bone Marrow depression Eosinophilia
Hepato-biliary disorders				Elevations in serum transaminase	
General disorders and administration site conditions		Peripheral oedema ¹ Fatigue			Somnambulism

Skin and subcutaneous tissue disorders		Exanthema ²			Stevens-Johnson Syndrome Dermatitis bullous Erythema multiforme Toxic epidermal necrolysis
Renal and urinary disorders					Urinary retention
Endocrine disorders					Inappropriate antidiuretic hormone secretion

¹ In clinical trials, these events occurred statistically significantly more frequently during treatment with mirtazapine than with placebo.

² In clinical trials, these events occurred more frequently during treatment with placebo than with mirtazapine, however not statistically significantly more frequently.

³ In clinical trials, these events occurred statistically more frequently during treatment with placebo than with mirtazapine

⁴ N.B. Dose reduction generally does not lead to less somnolence/sedation but can jeopardize antidepressant efficacy

⁵ Upon treatment with antidepressants in general, anxiety and insomnia (which may be symptoms of depression) can develop. Under mirtazapine treatment, development or aggravation of anxiety and insomnia has been reported.

⁶ Cases of suicidal ideation and suicidal behaviours have been reported during mirtazapine therapy or early after treatment discontinuation

⁷ The frequency of adverse reactions from spontaneous reporting, where no cases were observed in the randomised placebo controlled patient trials, are classified as 'not known'

In addition, any other symptom, side effect or adverse event listed in the Summary of Product Characteristics or the British National Formulary will not be regarded as unexpected.

13.4 Treatment Stopping Rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator, Regulatory Authority or Funder on the basis of new safety information or for other reasons given by the Data Monitoring Committee / Trial Steering Committee regulatory authority or ethics committee concerned.

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the Trial Steering Committee, who will advise on whether to continue or discontinue the trial and make a recommendation to the Sponsor. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected.

14 Statistics

14.1 Sample size

Our primary outcome is BDI score as a continuous variable. It is difficult to estimate a clinically important difference in BDI score, although the NICE guideline panel (7) have suggested that this corresponds to about 3 points (0.35 standard deviations) on the Hamilton Depression Rating Scale (28). The equivalent difference on the BDI total score would be 3-4 points (standard deviation 10-12 in COBALT trial). With 200 participants in each group, we would have 91% power to detect a difference of 0.33 standard deviations at the 5% level. Allowing for 15% loss to follow-up at 12 weeks, we will need to recruit 472 patients.

For our secondary outcome, response rate, defined as a 50% reduction in symptoms using the BDI score, 200 patients in each group would yield 90% power to detect a difference between 30% and 46% response, or an odds ratio of 2, at a 2-sided 5% significance level.

We will therefore plan to recruit 120 patients from 24 general practices at each of the four centres (Bristol, Exeter, Manchester/Keele and North East Yorkshire). This gives a target of 7 patients randomised per month per centre for the 18-month recruitment period. We have built in some flexibility with respect to resources across the 4 centres (section 7) so that we can take advantage of any opportunities for assistance with recruitment provided by the research infrastructure located at the four sites and to maximise recruitment relative to population size.

14.2 Randomisation

Stratifying by centre will ensure a balance in terms of local differences. Baseline BDI score and gender are important prognostic indicators and minimising on such variables will ensure a balance between the two groups. We will not exclude patients who have been referred for psychotherapy, either low intensity IAPT interventions or high intensity treatments such as CBT. These services are increasingly part of usual care in the NHS. However, we will minimise by current receipt of psychological services in order to balance the potential impact of access to other treatments that may be effective in this context. We would expect any benefit of better pharmacotherapy to occur whether or not the participant was also receiving psychological treatment.

14.3 Blinding and other forms of bias

Participants and investigators will be blinded to treatment. The effectiveness of blinding will be assessed by a questionnaire asking participants to which arm they believed they had been allocated at the 12-week follow-up. It is important that large pragmatic trials of pharmacological interventions for depression have a placebo arm, since the mean placebo response in treatment trials of Major Depression has been found to be close to 30% (29.) We have also used self-report instruments to assess outcomes in order to eliminate the potential for observer bias. Selection bias will be minimised by recruiting participants from a variety of practices based in rural, urban, affluent and deprived areas across the four centres. Exclusion criteria are minimal in order to maximise generalisability.

14.4 Data Analysis

Analysis and reporting will be in line with CONSORT guidelines (30), with the primary analyses being conducted on an intention-to-treat (ITT) basis. Descriptive statistics will be used to ascertain any marked imbalances in demographic or clinical variables at baseline.

The primary analysis will be the BDI score at 12 weeks post randomisation, measured as a continuous variable. The primary analysis will use linear regression to compare the groups as randomised, adjusting for stratification and minimisation variables and baseline measurements of the outcome. Secondary analyses of this outcome will include the BDI score at 12 weeks post-randomisation as a binary variable representing response, defined as a reduction in depressive symptoms of at least 50% compared to baseline, and remission, defined as a BDI score of less than 10. Secondary analyses will also include additional

adjustment for any prognostic variables demonstrating marked imbalance at baseline (ascertained using descriptive statistics).

In all analyses we will present regression coefficients (or odds ratios for binary outcomes), with 95% confidence intervals and p values.

We will also use repeated measures analyses incorporating the outcomes at 12 and 24 weeks and 12 months post-randomisation to examine whether any treatment effects are sustained or emerge later. This will be tested formally by the introduction of an interaction between treatment group and time. Finally, we will also investigate the influence of missing data using sensitivity analyses that make different assumptions, such as “best” and “worst” case scenarios, as well as using models to impute missing data. (31,32)

We propose to carry out per protocol analyses at 12 weeks and 12 months. These will only compare individuals who have remained on the trial medication at that follow-up point. We will also use the Complier Average Causal Effect (CACE) (33) approach. This provides an unbiased estimate of the treatment effect for those who have complied with the active treatment. This approach would be justified if the characteristics of those who adhered to the placebo differed from those that adhered to mirtazapine. This is plausible as we would expect intolerance of the side effects to be more important for the mirtazapine group and non-response to be more of an issue for the placebo group. If there is differential adherence in the two arms we will also investigate structural mean approaches to take account of this (34) though extensions of CACE to take account of adherence to placebo have also been developed (35).

At 12 and 24 weeks and 12 months, the ITT analysis will compare the randomised groups. By these stages, we would still expect many of those who had responded to mirtazapine to remain on the combination treatment. The ITT analysis will therefore provide an estimate of any longer term benefit attributed to the early response to mirtazapine with an SSRI/SNRI. The interpretation of this will depend upon whether other potentially active interventions are balanced between the groups. We do not expect to see many marked imbalances in other treatments, as our previous trials (IPCRESS, COBALT) have not found this to be a problem. If we do find that the groups differ markedly in the two arms we will investigate any possible impact of this by adjustment for the other interventions in the regression model.

A further sensitivity analysis using CACE methods could be used at 24 weeks and 12 months. If we define ‘compliers’ as those who had continued taking their trial medication up until 12 weeks, we could then estimate the effect of completing a 12 week course of mirtazapine on depression outcomes at the later follow-up points (6 & 12 months).

15 Economic Evaluation

Aim

The economic evaluation will assess the efficiency of mirtazapine plus SSRI or SNRI compared with SSRI or SNRI alone, for primary care patients with TRD. We will do this by valuing the relative costs and benefits of the combined therapy compared to SSRI or SNRI alone.

Background

Mirtazapine is inexpensive and is a well-established treatment for depression. Therefore if it is clinically effective as an additional treatment in this group of treatment resistant patients it is likely to be cost effective. However, differential resource use between the 2 arms during follow up is a possibility, perhaps associated with the potential for adverse reactions. This would make the intervention more expensive than it might first appear.

Ivanova et al (36) have found that direct and indirect costs for people with TRD are substantially higher than for major depressive disorder controls. Findings from the economic analysis should therefore be of value to NICE and to commissioners in estimating the initial affordability of treating TRD with mirtazapine and the probability and magnitude of future savings.

We also think it is important to have an accurate estimate of cost per QALY of various treatment options for TRD. We have cost-effectiveness estimates for the use of cognitive behavioural therapy in TRD from the COBALT trial. By collecting economic data in this trial we will be able to estimate the relative cost-effectiveness of mirtazapine versus other treatment options such as CBT.

Perspective

The two treatment strategies will be compared from the viewpoint of: (i) the National Health Service (NHS) and personal social services (PSS); (ii) patients and carers; and (iii) society. The analysis will be based on the costs incurred by the health service providers, patients and care-givers, and societal costs of time off work, at 12 weeks and 12 months after randomisation into each group.

Prior relevant work

Whilst there has been considerable work around calculating unit costs, there is little empirical data to inform the method of economic data collection. In the COBALT trial, we collected data on health service utilisation using a self-report questionnaire and also gathered data from primary care records. We will use both of these methods to estimate resource use. As primary care consultations are mainly with a non-specialist and it is often difficult to identify a precise reason for the encounter, we will include all such consultations regardless of whether they are clearly related to depression. For secondary care costs, we will initially include 'all cause' resource use, but will conduct a sensitivity analysis excluding resource use (for example, orthopaedic interventions) judged unlikely to be related to depression.

Data collection

This is informed by the COBALT study described above. Data on resource use will be collected from two main sources:

1. Practice records will provide information on: number of primary care consultations, by type e.g. face-to-face, telephone, etc. and who seen; and prescribed medication.
2. A questionnaire, administered at 12 and 24 weeks and 12 months, will provide information on: use of other primary and community care services (NHS Direct, attendances at walk-in centres, use of community health care services); secondary care related to mental health (number of out-patient visits, type of clinic, and reason for visit; inpatient stays, length of stay and reason); use of social services and disability payments received; personal costs related to mental health (expenditure on over-the-counter medication, expenditure on prescriptions, travel costs associated with health care visits, loss of earnings, out of pocket expenditure on other services e.g. private counselling or complementary and alternative therapies, child care and domestic help); time off work and unpaid activities (37).

The principle of opportunity cost will underlie the valuation of resource use though in many cases market prices will act as a proxy. The intervention will be valued using the mid-point salaries of staff and the cost of overheads. Recognised published sources will be used to value service use: Curtis & Netten (<http://www.pssru.ac.uk/uc/uc2011contents.htm>) for primary and community care consultations and the use of social services; national evaluations for consultations with NHS Direct and walk-in centres (<http://www.shf.ac.uk/content/1/c6/02/40/50/nhsd3.pdf>), DH tariff for A&E, OP and inpatient episodes (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459), and the British National Formulary (<http://www.bnf.org/bnf>) for prescribed medication. Time off work by patients and care-givers will be valued using the friction approach, which includes only the resources required to replace the employee.

Analysis

We will conduct: a cost-effectiveness analysis relating the costs of each strategy to the change in BDI scores at 12 weeks; a cost-effectiveness analysis relating the costs of each strategy to the change in depression scores at 12 months; a cost-utility analysis relating the costs of each strategy to QALYs gained, using the EQ-5D-5L-5L, at 12 months; and a cost consequences study relating the costs of each strategy from each perspective to changes in a portfolio of outcomes, at 12 months.

Discounting will not be necessary, as the costs and outcomes will cover a period of one year only.

The effect of uncertainty in unit cost estimates or assumptions about resource use will be addressed in sensitivity analyses. Uncertainty in the cost-effectiveness/utility ratios resulting from patient variation in resource use and effectiveness will be captured by estimating confidence intervals around the net benefit statistic and estimating cost-effectiveness acceptability curves.

16 Qualitative study

Aim

(i) Explore patients' views and experiences of taking either two antidepressant medications or an antidepressant and a placebo; (ii) identify patients' reasons for completing or not completing the study, including withdrawal from study medication; and (iii) to explore the views of general practitioners on prescribing a second antidepressant in this patient group

Background

We acknowledge that it is unusual to have a qualitative component in a pharmacological trial; we think this is a strength rather than a weakness and will provide valuable information for implementation in clinical practice. It allows us to explore certain areas in more depth than would otherwise be possible. We are testing a new combination of drugs rather than a new drug, and the attitude of both GPs to prescribing and patients to taking two antidepressants is of considerable importance. We do not know what patient attitudes to taking two antidepressants are; there may be considerable resistance. We do know that older people (who may be more likely to have depression that does not respond to an SSRI) can be reluctant to take antidepressants (38). Up until now combination antidepressant treatment has been mainly the preserve of psychiatrists, and the NICE guidance (Depression CG90) supports this, GP attitudes to the addition of a second antidepressant are also relevant. If the intervention is effective and cost effective it will be particularly useful to have a better understanding of the potential barriers, and facilitators to implementing combination antidepressant therapy as routine practice in primary care, and qualitative work will help us gain this understanding.

Recruitment and sampling

At the baseline assessment for the main study, individuals will be informed about the qualitative element of the trial and asked to consent to the possibility of being contacted by the qualitative research team to take part in an interview.

A purposeful sampling strategy will be used to identify potential interviewees to ensure interviews are held with participants in both arms of the trial, and with individuals in both arms who vary in their levels of adherence. Within this purposeful strategy, maximum variation sampling techniques will be used so that patients of different socio-economic background, gender and age are invited for interview. Patients will be sampled across the four centres.

Interviews will be held with patients after the primary outcome measure has been obtained (at 12 weeks post-randomisation) to avoid the possibility of bias that might be introduced by the qualitative interview having a supportive role. Individuals will be interviewed within 8 weeks of their primary outcome measures being taken.

In addition, we will ask patients who decline to participate, if they would be willing to be contacted by a researcher to discuss their reasons for not taking part in the trial.

Methods:

Qualitative methods will be employed to explore patient and professional experiences. Semi structured interviews will be used to elicit views on the perceived effectiveness and sustainability of the use of a second anti-depressant in the management of depression in primary care. Semi-structured interviews offer opportunities to cover, in-depth, a range of topics relevant to the research questions, but also allow for exploration and probing of issues raised during the interview.

Patient experience of taking two antidepressants for depression

In order to understand patients' views on depression and treatments offered, a nested qualitative study with patients participating in the trial will be conducted. A purposive sample of patients who have participated in the study will be invited to participate in a semi-structured interview, and perspectives on taking two tablets for depression will be explored. Patients who completed the 12-month intervention and who dropped out will be sampled. Interviews will be conducted either face to face or by telephone. The interviews will be taped with consent, transcribed, and the transcripts will form the data for analysis. It is anticipated that at least 24 interviews will be needed to achieve category saturation.

In order to understand why patients chose not to participate in the trial, a sample of decliners will be invited to take part in a short semi-structured telephone interview. Their views on the trial, and perspectives on taking two tablets for depression will be explored. The interviews will last 10-30 minutes and will be taped with consent, transcribed, and transcripts analysed. It is anticipated that at least 15 interviews will be needed.

General Practitioners' views on prescribing antidepressants for depression

In order to understand the potential barriers to prescribing of a second antidepressant in primary care, a nested qualitative study with general practitioners is proposed. A purposive sample of general practitioners (sampled on basis of practice demographics and size, experience and status (partner, salaried, locum) participating in the trial will be invited to participate in a semi-structured interview which will be taped (with consent). The interviews will be conducted either face to face or by telephone.

The interview will explore perspectives and views of GPs about managing people with depression, use of antidepressants and talking treatments, alternative approaches, switching antidepressants and referral options. The role of national guidelines (particularly about prescribing) in guiding individual management of a patient with depression will be explored. The interviews will be transcribed and the transcripts forming the data for analysis. It is anticipated that between 16 and 20 interviews will be needed to achieve category saturation of the data.

Data collection

Trial participants and GPs will be interviewed at a time and place that is convenient for them (e.g their home, GP surgery or by telephone). Written consent to take part in an interview will be obtained from participants and GPs at the time of face-to-face interviews, or prior to telephone interviews. These interviews will last about an hour. With participant consent, they will be audio-recorded and transcribed verbatim.

Analysis

Data will be coded by two researchers independently (CC-G and the appointed RA). Thematic analysis will be employed to identify and categories relevant and recurrent concepts within the data set, guided by the research questions of the study. Thematic analysis is guided by *a priori* concepts but also allows for qualitative data sets to be interrogated in an inductive manner. Themes are produced which unify the conceptual categories (39). Both data sets will be interrogated and re-analysed against the NPT framework (40) in order to consider how prescribing two anti-depressants may, or may not, be normalised into clinical practice.

17. Quality Assurance

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical trial data are credible. This research trial will be run in accordance with GCP.

17.1 Direct Access to Source Data / Documents

The Centre PIs and trial sites will allow monitors (from UH Bristol on behalf of the Sponsor), persons responsible for the audit, representatives of the Ethics Committee and of the Regulatory Authorities to have direct access to source data / documents. This is reflected in the Participant Information Sheet (PIS). Trial monitoring will be undertaken on behalf of the Sponsor by UH Bristol using their monitoring standard operating procedure http://www.uhbristol.nhs.uk/files/nhs-ubht/IS11-Monitoring_v3.5_15.09.2010.pdf

17.2 Trial Monitoring

17.2.1 Before the Trial

The Centre PIs and trial sites will allow the monitor to visit the site and facilities where the trial will take place in order to ensure compliance with the protocol requirements. The University of Bristol's Green Light procedure will be implemented in each of the other collaborating centres in order to document preparedness to conduct recruitment locally. A monitoring plan will be agreed prior to commencement of the trial.

17.2.2 During the Trial

The Centre PIs will allow the monitor and/or the Sponsor to:

- Inspect the site, the facilities and the material used for the trial;
- Meet all members of his/her team involved in the trial;
- Consult all of the documents relevant to the trial;
- Check that the CRFs have been filled out correctly;
- Directly access source documents for comparison of data therein with the data in the CRFs;
- Verify that the trial is carried out in compliance with the protocol and local regulatory requirements;
- Carry out trial monitoring at regular intervals, depending on the recruitment rate, and arranged between the CI and monitor;

All information dealt with during these visits will be treated as strictly confidential.

17.2.3 Quality assurance during the trial

The stages of quality assurance for the MIR trial will be as follows:

(i) The person completing the CRF checks their data entry is accurate.

The trial case report form (CRF) is the primary data collection instrument for the trial. All data requested on the CRF will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, "N/D" will be inserted. If the item is not applicable to the individual case, "N/A" will be inserted. All changes will be initialled and dated.

(ii) A random sample of 20% of CRFs will be checked, by the trial Research Team, against entries within the database for quality purposes.

The percentage checked will be increased if a significant error rate is found. In addition, the first five sets of recruitment data collected from a new site will be scrutinized.

(iii) Recruiting sites will be asked to perform a self-audit on all entries and provide a return to the Bristol trial centre (who will report to the Trial Sponsor).

(iv) A 10% sample audit will be conducted by the UH Bristol monitoring team, in line with the Service Level Agreement.

The structure of these audits will be agreed with the Sponsor and with the UH Bristol monitoring team.

The content of the database will be validated at two stages:

1. At data entry stage, validation rules will be set to run on submission of data in order to direct researchers to fields which require completion, should any essential fields have been missed, and to flag up anomalous or incomplete entries so that researchers can correct data prior to final submission of the electronic CRF;
2. Management information regarding data quality and completeness at centre, site and patient level generated from data within the trial database and used by the Trial Manager to inform the implementation and monitoring of the trial.

SOPs will be developed to address each aspect of quality control and quality assurance procedures.

18. Data Handling

Custodian: The Chief Investigator.

The database and randomisation system will be designed so as to protect patient information in line with the Data Protection Act 1998. Trial staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information at the trial centres. The participants will be identified only by a patient ID number on the CRF. All documents will be stored securely and made accessible only to trial staff and authorised personnel. The trial will comply with the Data Protection Act 1998 which requires data to be anonymised as soon as it is practical to do so.

Formal SOPs will be developed to detail each element of the data handling procedure.

A summary of the overall trial results will be made available to those participants who have confirmed that they wish to receive them, including GPs who have recruited to the study.

19. Data Management

Much of the baseline data (CISR and supplementary questions) will be entered directly into the computer by the participant, and will be transferred electronically into the trial database by the research associate. The remaining questionnaire data will be completed on paper by the participant or research associate and entered onto the study database in electronic form by the researcher. The system will incorporate data entry and validation rules to reduce data entry errors, and management functions to facilitate auditing and data quality assurance. All patients will be consented using paper consent forms. The trial centres will store the consent forms and paper CRFs until the end of the study, at which time they will be sent to Bristol for archiving.

Patient identifiers will be kept on a separate system from the clinical data and data protection requirements will be further enforced by best practice trial management procedures.

Following the end of the trial, the database will be cleaned and locked. SOPs will be developed to describe these processes.

At the outset of the trial an archiving plan will be developed. At the conclusion of the trial and after the database has been locked, all data will be archived for 15 years in accordance with the Sponsor's guidance and NIHR guidance. This will be in a secure location and available on request for audit and inspection by regulatory bodies. The Chief Investigator is responsible for authorising retrieval and disposal of archived material.

The location of the trial medicines will be tracked using the web-based database by all responsible personnel.

Formal SOPs will be developed for each aspect of trial data management and entry.

20. Publication Policy

An MIR publication policy will be developed in line with University of Bristol guidance within the first 12 months of the trial, and trial publications will be subjected to an independent quality assurance procedure (as per University of Bristol protocols).

21. Ethics and Regulatory Approvals and Reporting

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to Cardiff Panel C Research Ethics Committee (REC), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

Any subsequent protocol amendments will be submitted to the REC and MHRA, on the agreement of the Sponsor.

Annual progress reports will be submitted to the main REC. The first report will be submitted 12 months after the date on which the favourable opinion was given, and thereafter until the end of the trial. Progress reports will also be submitted to the funder in line with NIHR reporting requirements. Copies of these reports will be sent to the Sponsor prior to submission. Copies of all relevant reports will be made available to the DMC and TSC as appropriate.

Annual safety reports will be provided on the anniversary of the granting of CTA for the trial and sent to the MHRA and the main REC within 60 days of this date. A copy will be sent to the Sponsor prior to submission. An end of study declaration will be submitted to the REC and MHRA within 90 days of the end of the trial. A final report at conclusion of the trial will be submitted to the NIHR, the Sponsor, the REC and the MHRA within one year of the end of the trial.

22. Insurance Indemnity

The University of Bristol holds Professional Negligence insurance to cover the legal liability of the University, for harm to participants arising from the design of the research, where the research protocol was designed by the University.

The University of Bristol has arranged Public Liability insurance to cover the legal liability of the University as Research Sponsor in the eventuality of harm to a research participant arising from overall management of the research by the University of Bristol.

The other 4 Universities engaged in this project (Exeter, Manchester/Keele and York) have their own Public Liability insurance in place for their individual responsibilities. The University of Bristol's insurance policies do not provide an indemnity to any of our collaborators. As Research Sponsor The University of Bristol will ensure as far as reasonably practicable at the outset of the study that the other Universities involved hold appropriate legal liability insurance. These insurance policies do not indemnify individual GPs or their practices in respect of any clinical negligence on their part. The letter inviting GPs to participate in the trial specifically requires them to check with their medical negligence cover provider that they are insured to take part.

The insurance arranged by the University is in respect of serious injury to a research participant arising from participation in the trial; injury would include serious mental injury. It is however not possible to arrange insurance that would cover injuries to non-trial participants in the remote eventuality that a participant should injure someone else. The University's Public Liability insurance would cover the University of Bristol should it be held legally liable for such an eventuality but the normal rules of negligence (causation/foreseeability) would apply.

23. Financial Aspects

This trial is funded by the National Institute for Health Research, Health Technology Assessment Programme.

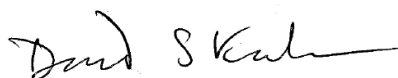
24. Investigative team expertise

A multidisciplinary research team from 4 centres (Bristol, Exeter, Manchester/Keele and York) supported by the NCRI-accredited Bristol Randomised Trials Collaboration, has been assembled with expertise covering RCT design, management & analysis (Kessler, Wiles, Lewis, Peters, Gilbody); primary care (Kessler, Campbell, Chew-Graham, MacLeod); psychiatry (Lewis, Dickens, Anderson, Gilbody); Psychopharmacology (Davies, Anderson); statistics (Peters, Wiles); qualitative methods (Chew-Graham, McLeod); and health economics (Hollingworth). Ian Anderson is lead author of the British Association for Psychopharmacology guidelines on the use of antidepressants in the treatment of depression and Chair of the NICE Clinical Guideline Development Group to revise the NICE depression guidelines.

25. Patient and Public Involvement

We have been in discussion with Mental Health Research Network (MHRN) in Bristol and PRIMER a PPI group based in Manchester in order to develop this aspect of the study. We have had feedback from both during the development of the protocol and support from both for the study in its current form. The MHRN has a structure for optimising patient and public involvement. We will use the West Hub (MHRN) Research Materials Advisory Service to help develop patient materials (e.g. PIS, consent forms etc). Study documents will be reviewed by a panel of service users who will offer constructive feedback on how to improve them. We recognise the importance of having service user representation on our trial steering group and at other relevant meetings. We have been put in touch with individuals who have lived experience of depression, and who are interested and knowledgeable about the research process. The MHRN has assisted us in identifying local depression support groups, where we plan to present the study and seek feedback. This will feed into plans around dissemination, or documents to assist with recruitment. Having made contact with this group, we have offered to return and present the study findings. This will help ensure that the results are reaching the people to whom they are most relevant. We will also make use of the MHRN reviewing service to help produce an easy to read summary of the findings to be sent to the study participants. A member of PRIMER will sit on the trial steering committee and this has been budgeted for.

26. Signatures



David Kessler
Chief Investigator

27. References

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28. Appendices

28.1 Appendix 1 - Trial Steering Committee terms of reference

1. To monitor and supervise the progress of the Mirtazapine as an addition to SSRIs for treatment resistant depression trial towards its interim and overall objectives, adherence to the protocol, adherence to the requirements of the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice, and to the principle that the rights, safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society;
2. To review at regular intervals new information of relevance to the research question (e.g. other related trials);
3. To consider the recommendations of the Data Monitoring Committee;
4. To provide a quality assurance function regarding trial process issues (e.g. protocol adherence);
5. To agree proposals for substantial protocol amendments (process to be developed by trial manager) and provide advice to the sponsor and funder regarding approvals of such amendments;
6. In the light of 1, 2 and 3, to advise the Chief Investigator, Trial Sponsor, Trial Funder, Host Institution and other relevant parties on all appropriate aspects of the trial;
7. In the light of 1, 2 and 3, to inform the NIHR Health Technology Assessment Board on the progress of the trial;
8. In the light of 1, 2 and 3 to provide advice to the investigators on all aspects of the trial.
9. To advise the TMG and the Funder (the NIHR HTA) on publicity and the presentation of all aspects of the trial.

28.2 Appendix 2 - Data Monitoring Committee terms of reference

1. To monitor the data from interim analyses, unblinded if appropriate, plus any additional safety issues for the Mirtazapine as an addition to SSRIs for treatment resistant depression trial and relevant information from other sources (including data emerging from other related studies);
2. To make recommendations following each meeting to the TSC on whether (the safety, rights and well-being of the trial participants being paramount) there are, in the light of 1., any ethical or safety reasons why the trial should not continue;
3. To determine if additional interim analyses of trial data should be undertaken, to consider any requests for release of interim trial data and make recommendations to the TSC on the advisability of this;
4. To provide a quality assurance function regarding trial data;
5. In the event of further funding being required, to provide to the Chief Investigator, TSC, Trial Sponsor or Trial Funder information and advice on the data gathered to date that will not compromise the integrity of the trial;
6. The Chair of the DM(E)C is directly answerable to the trial funder and to the trial sponsor;
7. The DM(E)C will be provided with the opportunity to seek input to data monitoring issues from the Patient / Public Representatives, if needed.

28.3 Appendix 3 – MIR Adverse Event Reporting Policy

See attached document

28.4 Appendix 4 - Centre Responsibilities

28.4.1 *Bristol centre* (in addition to the responsibilities of all centres):

1. Responsibility for obtaining trial-wide R&D and ethics approvals, and adhering to the standards of research governance as required by the trial Sponsor;
2. Management of the trial Investigational Medicinal Product;
3. Maintenance of the Trial Master File;
4. Development of all trial documentation and distributing these to the trial centres;
5. Overseeing the development, quality assurance and distribution of the trial medicines (Sharp Clinical Services will ship the medication packs to UHB Pharmacy, who will then organise delivery of the pack to individual patients. This distribution process will be overseen by the Bristol trial centre);
6. Development of the database and hosting infrastructure, including operationalisation (via the database) of the randomisation procedure
7. Development of trial-wide standard operating procedures and training protocols;
8. Working with the PCRN and MHRN SW clinical leads to explore the most effective strategies for maximizing recruitment to the trial;
9. Working with patient representatives to explore strategies for improving the acceptability of the trial treatment (should this prove to be a challenge to recruitment) and for minimising loss to patient follow-up in daily symptom diary completion;
10. Monitoring trial progress using management information provided by the trial database (accruals, follow-up rates, data completeness etc) and in response to qualitative feedback from the trial centres obtained through regular communications and trial management group meetings;
11. Co-ordinating initial and quarterly applications for Service Support Costs for local primary care sites (initial application, and quarterly reimbursements);
12. Monitoring the local research grant and ensuring the trial is conducted within the budget;
13. Co-ordinating regular meetings of the Trial Management Group, twice-yearly meetings of the Trial Steering Committee and Data Monitoring Committee, and other meetings regarding the governance or science of the trial, as required;
14. Conducting trial data analyses and writing first drafts of papers;
15. Producing reports for the funder, ethics committee, Sponsor and other boards as required, and reporting accruals to the UKCRN.

28.4.2 *All centres*: This list covers the main responsibilities of trial centres and is not exhaustive.

1. Working with local PCRN and MHRN to identify 24 suitable GP practices
2. Recruit 120 participants for the trial
3. Drug accountability;
4. Conducting GP site visits, explaining the trial to primary care clinical teams;
5. Entering data from paper collection forms onto the online database in a timely manner;
6. Ensuring site adherence to trial protocol;
7. Maintaining a centre site file with current versions of the protocol and trial documents, records of relevant R&D approvals and staff paperwork (GCP certificates, CVs, letters of access where appropriate), comprehensive documentation of any protocol deviations and auditing activities;
8. Administering Service Support Costs for local primary care sites in line with local CLRN schedules and procedures;
9. Reporting all AEs, SAEs and SUSARs within agreed timeframes.
10. Maintaining centre data for accruals, screening, withdrawals, SAEs and any corrections / changes to patient data.

28.5 Appendix 5 - Full schedule of questionnaires

Questionnaire	Postal screening	Baseline	2 weeks call	6 weeks	12 weeks	24 weeks	12 months
Consent form		Y					
BDI	Y	Y		Y	Y	Y	Y
Biographic and demographic data inc psych history, life events, social support, alcohol use	Y	Y					
Views on treatment		Y					
Medication	Y	Y		Y	Y	Y	Y
Morisky (adapted)	Y	Y		Y	Y	Y	Y
CISR		Y					
PHQ9		Y			Y	Y	Y
GAD7		Y			Y	Y	Y
EQ5D5L		Y			Y	Y	Y
SF12		Y			Y	Y	Y
Economics					Y	Y	Y
Health Events (SAEs)				Y	Y	Y	Y
ASEC		Y			Y		Y
2-week check			Y				
Blinding questions					Y		
Exit questionnaire							Y

28.6 Appendix 6 - Suicide Risk Protocol

See attached document

28.7 Appendix 7 - List of adequate doses for SSRI and SNRI antidepressants

Adequate Doses

A list of commonly used antidepressants with adequate doses for **MIR**

NAME	TRADE NAME	TYPE	BNF* CODE	MINIMUM ADEQUATE DAILY DOSE (MG)
CITALOPRAM	CIPRAMIL	SSRI	4.3.3	20
DULOXETINE	CYMBALTA / YENTREVE	SNRI	4.3.4	60
ESCITALOPRAM	CIPRALEX	SSRI	4.3.3	10
FLUOXETINE	PROZAC	SSRI	4.3.3	20
FLUVOXAMINE	FAVERIN	SSRI	4.3.3	100
PAROXETINE	SEROXAT	SSRI	4.3.3	20
SERTRALINE	LUSTRAL	SSRI	4.3.3	100
VENLAFAXINE	EFEXOR	SNRI	4.3.4	75

***Source:** BNF No.55 (March 2008) for BNF code and dosage

<u>Medical Abbreviations:</u>			
od	- once daily	om/m/mane	- in the morning
bd	- twice a day	on/n/nocte	- at night
tds	- three times a day	prn	- as required
qds	- four times a day		