NIHR HTA Programme

29 July 2013

The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

Health Technology Assessment Programme
National Institute for Health Research
Evaluation, Trials and Studies Coordinating Centre
University of Southampton, Alpha House
Enterprise Road, Southampton, SO16 7NS

tel: +44(0)23 8059 5586
fax: +44(0)23 8059 5639

email: hta@hta.ac.uk
web: www.hta.ac.uk

COBRA
(Cost and Outcome of BehaviouRal Activation):

A Randomised Controlled Trial of Behavioural Activation versus Cognitive Behaviour Therapy for Depression

Trial Protocol

Amendment History

List details of all protocol amendments here whenever a new version of the protocol is produced.

Amendment No.	Protocol version no.	Date issued	Author of change	Details of changes made
1	v2.0	11Dec2012	Rod Taylor	4.4 Randomisation

The COBRA Study is funded by:

NIHR HTA Ref: 10/50/14

Table of Contents

Chief Investigator: Prof Dave Richards[1]

Grant Co-applicants: Prof Simon Gilbody[2]
Prof Willem Kuyken[1]
Prof Rod Taylor[3]
Ms Emer O'Neill[4]
Dr Sarah Byford[5]
Prof Ed Watkins[1]
Dr Kim Wright[1]
Dr David Ekers[6]
Dr Dean McMillan[2]
Dr Heather O'Mahan[1]
Dr Paul Farrand[1]

Co-collaborators: Associate Prof Christopher Martell[7]
Assistant Prof Sona Dimidjan[8]
Prof Stephen Hollon[9]
Oxford Cognitive Therapy Centre[10]

1. *Mood Disorders Centre, Washington Singer Building, College of Life & Environmental Science, University of Exeter, Perry Road, Exeter, EX4 4QG*
2. *Department of Health Sciences, Seebohm Rowntree Building, University of York, Heslington, York, YO10 5DD*
3. *Peninsula Medical School, University of Exeter, Veysey Building, Salmon Pool Lane, Exeter EX2 4SG*
4. *Depression Alliance, Chief Executives Office, 20 Great Dover Street, London SE1 4LX*
5. *Institute of Psychiatry, Kings College London, De Crespigny Park, London SE5 8AF*
6. *Psychological Therapy, Tees, Esk & Wear Valleys NHS Foundation Trust, Newcastle Road, Chester le Street, Co Durham DH3 3UR*
7. *Department of Psychology, University of Washington, 818 12th Avenue, Seattle, 98122 Washington USA*
8. *Department of Psychology & Neuroscience, University of Colorado at Boulder, 345 UCB, Boulder, Colorado 80309-0345 USA*
9. *Department of Psychology, 306 Wilson Hall, 21st Avenue South, Vanderbilt University,2301 Vanderbilt Place, Nashville, Tennessee 37240-7817 USA*
10. *Oxford Cognitive Therapy Centre (OCTC), Warneford Hospital, Oxford OX3 7JX*

Email addresses:

Prof David Richards:	d.a.richards@exeter.ac.uk
Prof Simon Gilbody:	sg519@york.ac.uk
Prof Willem Kuyken:	w.kuyken@exeter.ac.uk
Prof Rod Taylor:	rod.taylor@pms.ac.uk
Ms Emer O'Neill:	emer@depressionalliance.org
Dr Sarah Byford:	s.byford@iop.kcl.ac.uk
Prof Ed Watkins:	e.r.watkins@exeter.ac.uk
Dr Kim Wright:	k.a.wright@exeter.ac.uk
Mr David Ekers:	david.ekers@tewv.nhs.uk
Dr Dean McMillan:	dm645@york.ac.uk
Dr Heather O'Mahan:	Ho215@ex.ac.uk
Dr Paul Farrand:	p.a.farrand@exeter.ac.uk
Associate Prof Christopher Martell:	martell@u.washington.edu
Assistant Prof Sona Dimidjan:	sona.dimidjan@colorado.edu
Prof Stephen Hollon:	steven.d.hollon@vanderbilt.edu
Oxford Cognitive Therapy Centre:	octc@oxfordhealth.ac.uk

1.0 Study Identifiers

1.1 Full title of trial

COBRA (**C**ost and **O**utcome of **B**ehaviou**R**al **A**ctivation): A Randomised Controlled Trial of Behavioural Activation versus Cognitive Behaviour Therapy

1.2 Acronym

'**COBRA**'

1.3 ISRCTN

Ref: ISRCTN27473954

1.4 HTA Reference

10-50-14

2.0 Study Background

2.1 Problem to be addressed

Clinical depression is one of the most common and debilitating of the psychiatric disorders. It accounts for the greatest burden of disease among all mental health problems, and is expected to become the second-highest amongst all general health problems by 2020.[1] Lifetime prevalence has been estimated at 16.2% and rates of co-morbidity and risk for suicide are high.[2-4] Depression is recurrent, and without treatment many cases become chronic, lasting over 2 years in 1/3 of individuals. Over 3/4 of all people who recover from one episode will go on to have at least one more.[5] In the UK, depression and anxiety are estimated to cost the economy £17bn in lost output and direct health care costs annually, with a £9bn impact on the Exchequer through benefit payments and lost tax receipts.[6]

Antidepressant medication (ADM) and CBT are the two treatments with most evidence of effectiveness; which are each recommended by NICE.[7] Problems with ADM include side effects, poor patient adherence and relapse risk on ADM discontinuation. Service-user organisations and policy think tanks advocate greater availability of psychological therapies, which many people prefer.[8] CBT, which is of similar efficacy to ADM,[9] has several advantages: a) it reflects the desire of many service users for non-pharmacological

treatment, b) it has no physical side-effects, and c) it modifies the illness trajectory in that benefits continue after the end of treatment, preventing recurrence. However, CBT has several disadvantages: a) its complexity makes it difficult to learn to implement in a competent fashion; b) its efficacy is dependent upon the skill of the individual practitioner; c) patients are required to learn quite high-level skills, d) the high costs of training and employing sufficient therapists limits access to CBT.

As a consequence of the problems above, many people do not receive adequate treatment, and even when treatment is given, many are refractory to the available interventions.[10] Despite the recent government initiative in England – 'Improving Access to Psychological Therapies' (IAPT) – no more than 15% of people with depression will receive NHS delivered CBT and only 50% will recover.[11] It is therefore important to continue to test promising new treatments, especially if there are indications that such treatments reduce the risk of symptom return; are applicable to a wide range of depressed people including those with high severity; are easy to implement in clinical practice and are therefore potentially more accessible[12] and cost-effective. Indeed, in order to meet public and professional expectations, the NHS requires a simple, equivalently effective, easily implemented psychological treatment for depression which can be delivered by less highly trained and specialised health workers to treat many more people with depression in a more cost-effective manner.

2.2 The need for a trial

Behavioural Activation (BA) is a psychological treatment alleviating depression by focusing directly on changing behaviour based on behavioural theory.[13-15] This theory states that depression is maintained by avoidance of normal activities. As people withdraw and disrupt their basic routines, they become isolated from positive reinforcement opportunities in their environment. They then end up stuck in a cycle of depressed mood, decreased activity and avoidance.[15] BA systematically disrupts this cycle, initiating action in the presence of negative mood, when people's natural tendency is to withdraw or avoid.[16,17] Although CBT incorporates some behavioural elements, these focus on increasing rewarding activity and initiating behavioural experiments to test specific beliefs. In contrast, BA targets avoidance from a contextual, functional approach not found in CBT – i.e., BA focuses on understanding the function of behaviour and replacing it accordingly. BA also explicitly prioritises the treatment of negatively reinforced avoidance and rumination. Furthermore, the BA rationale is easier to understand and operationalise for both patients and mental health workers than CBT; where activity is also increased but the primary techniques focus on changing maladaptive beliefs.[18] Moreover, CBT is less effective when delivered by less competent therapists.[9, 19] Thus, in the UK, CBT is delivered by senior NHS mental health workers with specialist training and a post-graduate qualification in CBT delivery, who are expensive to train and employ. The relative simplicity of BA treatment may make it easier and cheaper to train mental health workers in its application than CBT, the argument of 'parsimony' first advanced by one of the early proponents of this approach, Neil Jacobson, ten years ago.[15]

2.4 Limitations of previous trials

We conducted a meta-analysis of RCTs of BA,[20] where we first found a clinical effect size in terms of a reduced depression score of −0.70 SD units from twelve studies (n=459; 95% CI -1.00 to -0.39; p<0.001) comparing behavioural treatments to controls using experienced therapists (figure 1).

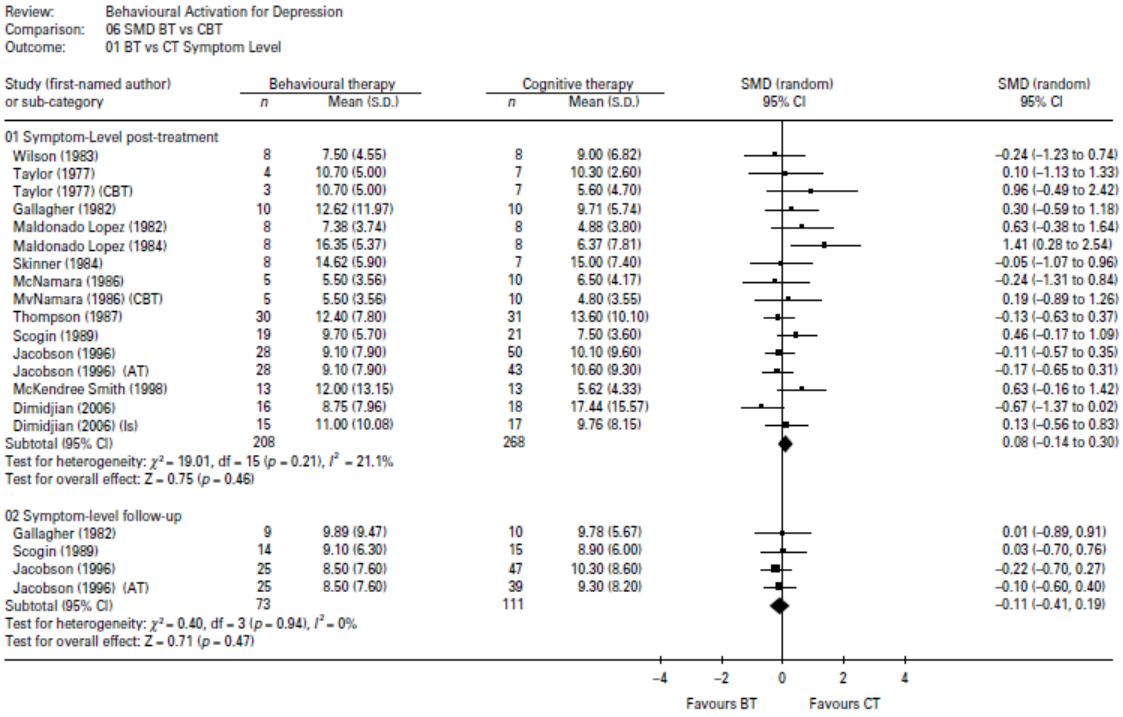

Figure 1

We then found twelve studies comparing behavioural treatments with CBT (n=476) and showed that behavioural treatments had equivalent outcomes to CBT (pooled SMD 0.08; 95% CI -0.14 to 0.30, p=0.46). In a subsequent meta-regression analysis, these behavioural treatments demonstrated a greater level of effectiveness at more severe levels of depression (meta-regression b-coefficient -0.05; 95%CI -0.10 to -0.01; p=0.04).

However, many of the trials were of limited methodological quality, all were under-powered for comparing treatments and most did not utilise diagnostic interviews for trial inclusion. Treatments in many cases did not conform to modern clinical protocols for BA. Long term outcomes were rarely reported with average follow-up only to four months. Therefore, the existing trial data are insufficient to provide certainty that BA should be a first line treatment for depression and these limitations led to NICE regarding the evidence for BA as equivocal and of insufficient strength to recommend BA for first-line routine NHS depression treatment.[7] Consequently, NICE [p256] made a clear research recommendation "*to establish whether behavioural activation is an effective alternative to CBT*" using a study which is

"*large enough to determine the presence or absence of clinically important effects using a non-inferiority design*".[7]

In order to test uncertainties around our main COBRA hypothesis – that BA will be equivalently effective to CBT and more cost effective – we piloted BA in a phase II RCT to examine the parsimony argument directly, i.e. whether generic mental health workers, without previous experience in therapy, can effectively treat depressed people using a full high-intensity BA therapeutic protocol.[21] We compared BA against usual care. BA was delivered by NHS AfC grade 5 mental health workers with no previous formal training or psychotherapeutic experience, who received five days training in BA and subsequent one hour clinical supervision fortnightly from David Ekers (nurse consultant, educator and COBRA applicant). Intention to treat analyses (figure 2) indicated a difference in favour of BA of −15.79 (n=47; 95% CI −24.55 to −7.02) on depression (Beck Depression Inventory-II), an effect size of −1.15 SD units (95% CI − 0.45 to −1.85). This compares favourably to the overall effect size of −0.70 comparing BA to controls using experienced therapists in our meta-analysis above.[20] The mental health workers demonstrated excellent fidelity to the protocol when audio recordings were assessed by independent accredited cognitive behavioural therapists with extensive experience in BA.

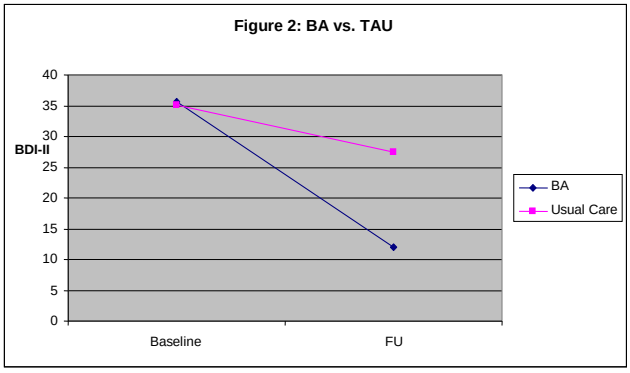

Figure 2

2.4 Research objectives

The COBRA programme of research seeks to answer two interlinked questions:

1. What is the clinical effectiveness of BA compared to CBT for depressed adults in terms of depression treatment response measured by the PHQ9[22] at 12 and 18 months?
2. What is the cost-effectiveness of BA compared to CBT at 18 months?

In addition, we will undertake a secondary process evaluation to investigate the moderating, mediating and procedural factors in BA and CBT which influence outcome.

3.0 Study Design

3.1 Trial outline

COBRA is a two-arm Phase III, non-inferiority randomised controlled trial for people with depression to test the effectiveness of a psychological intervention for depression – Behavioural Activation (BA) – against the current gold standard evidence-based psychological treatment recommended by the National Institute for Health and Clinical Excellence (NICE) – Cognitive Behaviour Therapy (CBT). COBRA includes clinical, economic and process evaluations. We need to know whether BA represents a viable first choice of treatment in the management of depression. In this sense we will need to establish whether the clinical effectiveness of BA is not substantially inferior to CBT. Accordingly, we have powered our trial on the basis of clinical non-inferiority, and will analyse our data accordingly (see section 3.7.1).[23, 24] Our primary end point for analysis will be at 12 months follow-up, but we will also conduct an interim analyses at 6 months and an 18 month analysis to investigate relapse rates and retention of treatment effects. Our final 18 month follow-up point is the longest we can realistically achieve in a trial of this nature, although if the trial is successful, we plan to bid for further funds to conduct analyses beyond this end-point.

Phase II evidence shows that BA can be effective when delivered by mental health workers with a less expensive, short, compact and targeted training who are working at a lower Agenda for Change (AfC) salary banding than those currently employed to deliver CBT. We hypothesize, therefore, that BA is non-inferior compared to CBT in reducing depression severity but that BA will be less costly and thus more cost-effective than CBT. We will examine the cost-effectiveness of treatment with BA compared to CBT in terms of cost per quality adjusted life years gained. Primary economic evaluation will take the NHS/Personal Social Services Perspective in line with NICE guidelines.[25] Secondary analysis will take a broader perspective including productivity losses as a result of time off work due to illness, known to be a substantial cost in depression.[26] Economic analyses will be at 18 months to best capture the economic burden of depression.

An RCT provides the opportunity to test the theory that underpins BA and CBT and explore how it can be optimised. Process evaluation nested within a trial can be used to assess fidelity and quality of implementation, clarify causal mechanisms and identify contextual factors associated with variation in outcomes.[27] We will, therefore, embed a series of exploratory quantitative and qualitative studies to investigate the moderating, mediating and procedural factors in BA and CBT which influence outcome in line with the MRC Complex Interventions Framework[27] (see 3.8.4).

3.2 Trial interventions

We have specified our BA & CBT interventions in line with (a) the original treatment protocols[9,16-18,28] and (b) NICE recommendations[7] for duration and frequency of BA and CBT. The key components of BA and CBT will be monitored through observation of therapy recordings (section 3.7.3). Protocols will also include recommendations for managing comorbidity, particularly anxiety.

3.3 Behavioural Activation (BA): Participants will receive a maximum of 20 sessions over 16 weeks with the option of four additional booster sessions.[7] The overall goal of BA is to re-engage participants with stable and diverse sources of positive reinforcement from their environment and to develop depression management strategies for future use. Sessions will be face to face, of one-hour duration, with the option of being conducted up to twice weekly over the first two months and weekly thereafter. They will consist of a structured programme increasing contact with potentially antidepressant environmental reinforcers through

scheduling and reducing the frequency of negatively reinforced avoidant behaviours. Treatment will be based on a shared formulation drawn from the behavioural model in the early stages of treatment, thereafter developed with the patient throughout their sessions. Specific BA techniques include the use of a functional analytical approach to develop a shared understanding with patients of behaviours that interfere with meaningful, goal-oriented behaviours and include self monitoring, identifying 'depressed behaviours', developing alternative goal orientated behaviours and scheduling. In addition the role of avoidance and rumination will be addressed through functional analysis and alternative response development incorporating recent trial evidence by applicant Watkins.[29, 30] Mental health workers delivering BA will follow a revised treatment manual based on that used in our Phase II trial[21] and previous international studies,[28] incorporating recommendations from NICE Guidelines[7] and advice from our international collaborators, Martell and Dimidjan.
Workers will be selected from NHS AfC grade 5 mental health workers such as mental health nurses and Psychological Wellbeing Practitioners and will receive five days training in BA. In line with the programme developed and tested in our Phase II trial,[21] training will focus upon the rationale and skills required to deliver the BA protocol for depression and include sections on behavioural learning theory and its application to depression, developing individualised BA formulations and specific techniques used in sessions. Training will be a mix of presentation and role play with repeated practise and feedback. Workers will be competency-assessed at the end of training and further training given if competency is not demonstrated in practical clinical exercises. BA workers will receive subsequent one hour clinical supervision fortnightly from the three site leads or other clinically qualified members of the trial team.

3.4 Cognitive Behaviour Therapy (CBT): participants will receive a maximum of 20 sessions over 16 weeks with the option of four additional booster sessions. The overall goal of CBT is to alter the symptomatic expression of depression and reduce risk for subsequent episodes by correcting the negative beliefs, maladaptive information processing and behavioural patterns presumed to underlie the depression Sessions will be face to face, of one-hour duration, with the option of being conducted up to twice weekly over the first two months and weekly thereafter. They will consist of a structured, partially didactic programme. Treatment begins with patients learning the model, behavioural change techniques, and moves on to to identifying and modidfying negative automatic thoughts, maladaptive beliefs and underlying core beliefs. In later sessions, learning is translated to anticipating and practicing the management of stressors that could provoke relapse in the future. Specific CBT techniques include scheduling activity and mastery behaviours, the use of thought records and modifying maladaptive beliefs. The behavioural elements in CBT focus on increasing activity together with practical behavioural experiments to test specific cognitive beliefs. CBT will not take the contextual, functional approach of the BA trial arm, nor will CBT explicitly prioritise the targeting of avoidance and rumination. Therapists delivering CBT will follow a treatment protocol based on the standard manuals published by Beck and colleagues.[18,31] and including additional advice and training resources from our US collaborator, Steve Hollon from Vanderbilt University.

CBT will be delivered by senior mental health workers with a specialist postgraduate diploma in 'high-intensity' CBT from an accredited University course. These workers are employed as NHS AfC grade 7. They will also receive a five day orientation training to the specific CBT protocol[18, 31], including its adaptation for co-morbidities, cognitive theory of depression, developing individualised cognitive formulations and specific techniques used in sessions. Therapists will be competency-assessed at the end of training and further training given if

competency is not demonstrated in the specific CBT protocol to be used. CBT therapists will receive subsequent one hour clinical supervision fortnightly from established supervisors in the three sites with advice from other

4.0 Sample

4.1 Inclusion and exclusion criteria

Inclusion: People aged 18 and older with DSM Major Depressive Disorder assessed by standard clinical interview (Structured Clinical Interview for Depression –SCID).[32] Researchers will be trained to administer the SCID using established training and inter-rater reliability procedures in use at the Mood Disorders Centre for all our trials.

Exclusion: People who are alcohol or drug dependent, acutely suicidal or cognitively impaired, have a bipolar disorder or psychosis/psychotic symptoms, ascertained by baseline research interviews. We will also exclude people currently in receipt of psychological therapy.

4.2 Sample size calculation

We have estimated the non-inferiority margin for the primary outcome (PHQ 9) using two potential approaches: (1) with reference to the effect size of historical trials comparing BA versus control and (2) with reference to the published minimally important clinical difference (MICD) for the primary outcome (PHQ9) of 2.59 to 5.00.[33] Based on the meta-analysis presented in figure 1, BA was superior to control in depression score by a mean of 0.7 SD units (95% CI: 0.39 to 1.00) or 3.8 (2.1 to 5.4) on PHQ9 score units (assuming an SD of 5.4 from Lowe and colleagues).[33] It has been proposed that non-inferiority margins be taken as ~0.5 x mean control effect size (i.e. 0.5 x 3.8 =1.90) or as the lower 95% limit of the control effect size (i.e. 2.1).[34,35] To ensure the adequacy of this trial to test non-inferiority between BA and CBT, we therefore examined a number of potential scenarios taking in account the potential uncertainty in the non-inferiority margin for the primary outcome (see table below).

Approach	MICD	Power	Attrition rate	Sample size per group*
50% BA-control effect size	1.90	90%	20%	220
50% BA-control effect size	1.90	80%	20%	160
LCI BA-control effect size	2.10	90%	20%	180
LCI BA-control effect size	2.10	80%	20%	135
Lower MCID	2.59	90%	20%	120
Lower MCID	2.59	80%	20%	90

*Calculated assuming PHQ9 SD of 5.4[33] & 1-sided 2.5% alpha using NQuery v7.0 MTE0-6

We have selected a conservative non-inferiority margin of 1.90 and power of 90%. As a consequence, we will need to recruit a total of 440 participants to detect a between group non-inferiority margin of 1.90 in PHQ9 at 1-sided 2.5% alpha, allowing for 20% attrition caused by drop outs and protocol violators (see section 3.7.1). Furthermore, although

previous trials of CBT have shown little or no effects of clustering in outcome by therapists, even when delivering group CBT[36,37], if we were to assume a small therapist clustering effect (i.e. intra-cluster correlation coefficient of 0.01) this sample size would still have 80% power for a non-inferiority margin of 1.90 in PHQ9 at 1-sided 2.5% alpha, allowing for 20% attrition.

Our sample size is inflated by 20% for participant drop out to take account of those that exit the trial and refuse follow-up assessment, although our experience running large primary care trials of depression treatment [COBALT, CADET] is that attrition rates will be less than this. Therefore, we intend to recruit 440 participants to the trial, 220 per arm.

4.3 Recruitment

Randomised controlled trials are vulnerable to selection bias and threats to external validity if there are systematic differences in behaviour between referring clinicians. We will minimise this potential bias by recruiting participants through searching GP records, rather than by direct GP referral. Our experience from our previous and current recruitment data (CADET, PREVENT, COBALT) is that around 21% of potential participants identified through case note searching will finally be interviewed by our research team following a letter and/or telephone reminder.

Similarly, from previous trials experience we calculate that 37% of potential participants who are interviewed at baseline are likely to decline participation, will not meet our inclusion criteria or will meet one of the exclusion criteria. Therefore, our research team will need to interview 700 potential participants in order to induct our planned sample size of 440 eligible participants into the trial. Following random allocation of 440 participants, a maximum of 20% attrition will lead to our target sample size of 366 participants

In order to identify 700 people for baseline interview, we will need to contact around 3,400 potential participants through letter and/or telephone to inform them of the trial and offer them the chance to participate. In order to do so, we must identify 5,300 potential participants from a sensitive READ code search of practice case-note records, since our existing data would predict that 1,900 (approx 36%) of these will be excluded by GPs against known trial exclusion criteria. Identifying 5,300 potential participants will generate at least 700 positive replies.

For an average size practice of 7,000 registered patients our experience is that searches will be likely to identify around 37 potentially eligible participants per search. Four searches per practice will, therefore, identify 148 potential participants per practice. Consequently, we need 36 practices (12 per site) to identify sufficient potential participants to meet our target number of 5,300.

A further threat to any study's external validity arises from the poor response rates when participants are asked to return paper trial enrolment forms. This is particularly true for depression trials where the symptomatic presentation of depression is characterized by lack of volition, energy, anhedonia and hopelessness. A review of RCT recruitment methods[38] showed that the only likely method of improving recruitment was through telephone reminders to those potential participants not responding to an initial letter. Consequently, we have used this method in the CADET and PREVENT trials. In CADET approximately twice

as many people consent to be interviewed via the telephone follow up route than through returning a letter.

Therefore, in order to maximise our recruitment rate, we will adopt the following procedures. We will identify suitable participants by examining electronic case records for all patients in each general practice. The search will be limited to people seen by their GPs in the previous two months who have been allocated a 'Read Code' for depression, and will be conducted by practice staff or Research Network Clinical Studies Officers. The list of potentially suitable participants will be reviewed by GPs to identify any patients whom have known exclusion criteria. The remaining patients will be written to, inviting them to take part in the study. Letters will be accompanied by a short participant information sheet, stamped addressed envelope and a 'Permission for Researcher to Contact' form to allow a researcher to contact them. If potential participants do not return the form, they will be contacted by telephone by practice staff or practice based Research Network Clinical Studies Officers to check they have received the letter and asking them if they wish to participate in the COBRA trial. Telephone calls will be sensitively conducted, people will be fully informed of their rights to refuse to participate without adverse consequences and there will be no coercion into joining the trial. If the potential participant wishes to speak to a researcher, permission will be obtained for contact details to be passed onto the research team. Research staff will not contact the potential participant until 48 hours have elapsed since the initial phone call, to allow the person to reflect and change their mind if they so wish. Potential participants identified by either written or telephone routes will be interviewed by researchers to assess eligibility, to have the trial fully explained and answer any questions from the participant. If eligible, fully informed and consenting they will be entered into the study and randomization.

4.4 Randomisation

Participants will be allocated in a 1:1 ratio to either BA or CBT arms stratified according to their symptom severity (PHQ9 < 19 vs >=19), antidepressant use (currently using anti-depressants or not) and site (3 in Exeter, 2 in Durham and 2 in Leeds). A computer based system will allocate the first 20 participants to each arm on a truly random basis. For subsequent participants, allocation will be minimised to maximise the likelihood of balance in stratification variables across the two study arms. Concealment will be ensured by use of a password-protected trial website and retaining a stochastic element to minimisation algorithm. The computer-based allocation and website will be setup and maintained by UKCRC accredited Peninsula Clinical Trials Unit, independent of the trial.

Following screening, each participant will be assigned an ID number. Using this ID number and information on their stratification variables, the trial manager will log into website in order to allocate each participant to either BA or CBT arm of the trial. Once allocation has been made, the trial manager will then select the therapist allocated to the patient at each site based on the therapist workload. The trial manager will have no direct knowledge of the therapists or their outcomes. The participant's details will be sent to the relevant mental health worker to alert them to contact this person. The GP of all new participants' will be informed of their involvement in the study. We have used this randomisation system successfully in other trials (CADET[39], PREVENT[40]) we are conducting.

4.5 Blinding

All research measures will be applied to both groups of participants equally. Researchers will be blind to group allocation, which will occur after baseline assessments. At follow up, researchers will be instructed to maintain blindness by reminding participants of the confidential nature of their treatment and the need not to discuss this with researchers. We will test blindness by asking researchers to indicate at follow up which treatment they believe the participants received and analyse any correlation with outcome. We will follow up participants at 6, 12 and 18 months. We will use multiple methods to maintain contact with participants over this extended follow up period. In previous trials of depression treatments we have achieved 85-95% follow up rates. This has been achieved through providing sufficient resource to facilitate researchers making multiple attempts and using multiple methods to contact and interview participants (telephone, letter, email, personal visits). Close monitoring and trial management support from a full time trial manager is essential for this to work well. We will update our participant contact records frequently by contacting general practices and ensuring participant contact details are up to date. We will work with primary care and GP consortia information managers to ensure our records are current. Participants are, of course, free to withdraw from the trial at any point and any participants who withdraw from the trial will be the only ones not followed up in the manner described above. We will compare the baseline characteristics of drop outs and those lost to follow up with completers and undertake sensitivity analyses to take account of the effects of any missing data.

4.6 Follow-up

We will conduct follow up assessments at six, twelve and 18 months, our primary analysis comparing primary and secondary outcomes between BA and CBT groups at 12 months adjusting for baseline outcome values and stratification variables (symptom severity, site, antidepressant use) and fitting therapist as a random effects variable.

5.0 Data Collection and Analysis

5.1 Primary outcome measure will be self reported depression severity as measured by the PHQ9.[22] The PHQ9 is a measure of depression widely used in clinical trials, clinical practice and as part of the NHS Quality and Outcomes Framework for primary care with established excellent specificity and sensitivity characteristics in a UK population.[41]

5.2 Secondary outcome measures: DSM depression status and depression free days;[32] Health Related Quality of Life (SF-36).[42]

5.3 Economic data: Quality adjusted life years (QALYs) calculated using the EQ–5D measure of health-related quality of life.[43] Participants' use of BA and CBT will be collected from clinical records, with information on additional resources involved (e.g. training, preparation, supervision etc.) collected directly from therapists. All other health and social care services used, including medication prescription and use, and productivity losses will be measured using the Adult Service Use Schedule (AD-SUS), based on previous evidence of

service use in depressed populations.[44] Productivity losses will be measured using the absenteeism and presenteeism questions of the World Health Organization's Heath and Work Performance Questionnaire (HPQ).[45] Intervention costs will be calculated using a standard micro-costing (bottom-up) approach,[46] and will be based on therapist salaries plus on-costs (employers national insurance and superannuation contributions) plus appropriate capital, administrative and managerial overheads. Costs for NHS hospital contacts will be taken from NHS reference costs. Nationally applicable unit costs will be applied to all community health and social care contacts.[47] The cost of medications will be taken from the British National Formulary.[48]

5.4 Process data: Age of depression onset and number of previous episodes (assessed with the SCID), changes in specific behaviour, learned capacity to apply behavioural principles to modify the environment, changes in beliefs, changes in underlying information processing style, acceptability of BA and CBT for participants and clinicians (assessed with the qualitative process studies), per-protocol treatment adherence. Qualitative data will be collected via semi-structured interviews and written responses to access participants' accounts of the mechanisms and impacts of treatment. At the end of treatment, all participants will write short accounts of their experiences of and perceived impacts of treatment in response to open-ended questions. Additionally, at trial end, semi-structured interviews designed to obtain a more in-depth understand of the ongoing mechanisms and impact of treatment will be conducted with purposively sampled participants and therapists building on the analysis of the written accounts. Interviews will focus on the participants' views of the role of cognitive and behavioural change strategies and broader impacts of treatment in participants' lives. Integration with the quantitative process data will enhance understanding of change mechanisms that can improve these treatments' potential efficacy.[49,50]

6.0 Statistical analysis

6.1 Clinical Outcomes

All analyses will be carried out using an a priori statistical analysis plan prepared in the first 6 months of the trial and agreed with the TMG, TSG and DMC in accord with reporting guidelines for non-inferiority and equivalence trials.[24] In a superiority trial, intention-to-treat (ITT) analysis is conventionally used as the most conservative approach to minimise the possibility of a type I error, i.e. falsely concluding that one treatment is superior to another. ITT includes data in the primary analysis from participants who drop out or violate the protocol to ensure differences between treatments under test are not falsely inflated and ensuring the most rigorous conditions apply before rejection of the null hypothesis (i.e. treatment A is not superior to treatment B). However, in non-equivalence trials the null hypothesis is the opposite, and states that the experimental treatment is ***inferior*** to the reference treatment. CONSORT guidelines for such trials,[24] recommend analyses to maximise the chances of finding a difference between treatments ensuring stringent conditions apply before rejection of the specific non-inferiority null hypothesis. Paradoxically, because conventional ITT analysis tends to bias towards not finding a difference, adopting an ITT approach could make the null-hypothesis easier to reject in non-inferiority trials by a "*blurring of the difference between the treatment groups* [which] *increases the chance of finding equivalence*"[51] i.e. a false non-inferiority result (type I error). Whilst the CONSORT guidelines recommend a per-protocol (PP) approach (i.e. analysis according to actual

treatment received) as the conservative non-inferiority analysis option, given the potential biases of both PP and ITT analyses, we agree with the European Agency for the Evaluation of Medicinal Products that security of inference depends on **both** PP and ITT analyses demonstrating non-inferiority of the primary outcome.[35] We will, therefore, check for non-inferiority in PP and ITT populations, conducting sensitivity analyses on the primary outcome for PP and imputed ITT populations to check the security of inference of non-inferiority. We will also conduct sensitivity analyses using different definitions of PP adherence. We will include varying proportions of PP participants in these sensitivity analyses populations, depending on how much of each therapy they have received, ranging from 40-100% of planned therapy sessions. If non-inferiority is consistently shown by these analyses, we will proceed to assess superiority of CBT vs. BA, i.e. the CI lower bound lies above 0.

The 1-sided 97.5% CI for the between group difference will be estimated and non-inferiority of BA compared to CBT will be accepted (in a 0.025 level test) if the lower bound of the 97.5% CI lies within the non-inferiority margin of -1.90 in PHQ9 score. If non-inferiority is shown, we will then test for superiority of CBT over BA (i.e. lower bound of the 97.5% CI lies above 0). We will also check for non-equivalence at all follow-up points using the same approach. Secondary analyses will be undertaken to compare groups at follow up across 6, 12, 18 months using a repeated measures approach. The analysis will be extended to fit interaction terms to explore possible differences in treatment effect in baseline symptom severity and antidepressant usage. Sensitivity analysis, making different assumptions about the imputation model used will be conducted for both primary and secondary analyses to assess the likely impact of missing data. Models will be fitted using generalized linear mixed models and undertaken in STATA v.11

6.2 Economic analysis

Analyses will compare the costs and cost-effectiveness at the final 18-month follow-up of BA and CBT to capture the economic impact of events such as relapse, although we will conduct an initial preliminary analysis at 12 months to coincide with the primary clinical analyses. Although the distribution of costs is commonly skewed in populations of this kind, analyses will compare mean costs using standard parametric t-tests with covariates for pre-specified baseline stratification factors plus baseline costs. The robustness of the parametric tests will be confirmed using bias-corrected, non-parametric bootstrapping.[52,53] quality adjusted life years (QALYs) calculated using the EQ–5D measure of health-related quality of life.[43]

Whilst studies designed to test equivalence of effects are considered to be a legitimate situation in which a cost-minimisation analysis (CMA), where costs alone are compared given equal outcomes, may be appropriate,[54] the same may not be true for non-inferiority designs. Even in situations where equivalence or non-inferiority are demonstrated, exploration of the joint distribution of costs and effects in a cost-effectiveness analysis (CEA) is recommended to represent uncertainty[54] and to help interpret the economic results.[51] For these reasons, we propose to undertake a CEA irrespective of whether or not non-inferiority in the primary clinical outcome is demonstrated. Cost-effectiveness will be assessed using the net benefit approach[55] with reference to Bosmans' methods[51] for economic evaluations alongside equivalence or non-inferiority trials. Effects for CEA will be explored in terms of QALYs and the primary analysis will be carried out at the 18-month follow-up point to capture differential effects associated with relapse and will take the NHS/Personal Social

Services perspective preferred by NICE.[25] Secondary analysis will include productivity losses as a result of time off work. Uncertainty around the cost and effectiveness estimates will be represented by cost-effectiveness acceptability curves.[56,57] A joint distribution of incremental mean costs and effects for the two therapies will be generated using non-parametric bootstrapping to explore the probability that each of the treatments is the optimal choice, subject to a range of possible maximum values (ceiling ratio) that a decision-maker might be willing to pay for an additional QALY gained. Cost-effectiveness acceptability curves will be presented by plotting these probabilities for a range of possible values of the ceiling ratio,[58] a recommended decision-making approach to dealing with the uncertainty that exists around the estimates of expected costs and expected effects associated with the interventions under investigation and uncertainty regarding the maximum cost-effectiveness ratio that a decision-maker would consider acceptable.[57,59]

6.3 Process Evaluation

Based on recent reviews,[60] exploratory moderational analyses will examine baseline variables that might moderate outcome at multiple time points (6, 12 and 18 months) across the two treatments including: depression severity, age of depression onset, number of previous episodes, and baseline levels of cognitive and behavioural dysfunction, using the approach set out by Kraemer et al.[49] Although the power to detect moderate subgroup interactions will be low, we are primarily interested in exploring the possibility of large interactions that could inform subsequent clinical decision-making re: treatment allocation.

Mediational analyses will investigate the hypothesised mechanisms of change (for BA: changes in specific behaviour such as reduced avoidance and rumination, learned capacity to apply behavioural principles to modify the environment; for CT: changes in beliefs and underlying information processing style) pre-treatment to mid-treatment, mid-treatment to post-treatment across the trial arms using approaches to testing mediation that allow multiple mediators in one model.[49] We will also analyse audio recordings of BA and CT sessions to assess changes in putative mediators amongst patient and therapist within-session behaviour.[50] The effects of the mediators on outcome at 12 and 18 months will be modelled. This approach to examining mediation ensures that changes in putative mediators temporally precede changes in the primary outcome and allow baseline to-post-treatment change in symptoms to be statistically controlled, necessary to rule out reverse causality. This approach has been successfully used by members of our group in mechanisms research.[61] Analyses will include multivariate growth models including autoregressive and lagged terms, as well as recent developments in mediator analysis that use instrumental variables (IVs) to account for the effect of unobserved confounding on mediators – we will follow precedent in using treatment allocation and its interaction with baseline measures as IVs.[62] These assessments will comprise validated questionnaire (e.g. Behavioural Activation for Depression Scale;[63] Dysfunctional Attitude Scale[64]) coding schemes, and cognitive-experimental measures of the variables that we hypothesise mediate CT and BA's effects.

6.4 Qualitative data analysis

Qualitative data will be analysed using a framework analysis[65] combining inductive and deductive approaches and will be conducted collaboratively by a small sub-group of the

research team led by principal applicant Richards who is experienced in using this approach.[66] Thematic frameworks will be developed to identify key concepts and themes and interview transcripts will be examined thematically across the whole data set as well as in the context of each interview, using a constant comparative analysis approach.[67] Data will be indexed, rearranged and mapped onto the identified themes and subthemes and interpreted and reanalyzed within the thematic framework to distil, interpret and structure component statements, the original transcripts being frequently revisited to clarify contextual meaning.

7.0 Ethical Issues

7.1 Anticipated risks and benefits

No treatment will be withheld from participants taking part in this trial. Both arms are active psychological treatments with previously demonstrated efficacy and no known iatrogenic effects. This trial may in fact benefit individual participants, since CBT is only available for 8-15% of people with depression. By participating in this trial, participants will also receive an intensive level of monitoring such that any participants worsening or at suicidal risk will be identified and directed to appropriate care.

7.2 Informing participants of anticipated risks and benefits

Participant information leaflets will provide potential participants with information about the possible benefits and known risks of taking part in the trial. Participants will be given the opportunity to discuss this issue with their GP or the trial manager prior to consenting. The trial manager will inform the participant if new information comes to light that may affect the participant's willingness to participate in the trial.

7.3 Obtaining consent

Potential participants will receive an information pack about the trial, including a participant information sheet, stamped addressed envelope and a 'Permission for researcher to contact' form to allow a researcher to contact them. The information leaflets will be produced using the current guidelines for researchers on writing information sheets and consent forms, posted on the UK ethics website, and informed by our consumer/lived experience user representatives. Participants who wish to partake in the trial will return their initial consent to be contacted form to the site research team. If people do not return the form, they will be contacted by telephone by practice staff or practice based Research Network Clinical Studies Officers to check they have received the letter and asking them if they wish to participate in the COBRA trial. Telephone calls will be sensitively conducted, potential participants will be fully informed of their rights to refuse to participate without adverse consequences and there will be no coercion into joining the trial. If the person wishes to speak to a researcher, permission will be obtained for contact details to be passed onto the research team. Research staff will not contact the potential participant until 48 hours have

elapsed since the initial phone call, to allow the person to reflect and change their mind if they so wish. Potential participants identified by either written or telephone routes will be interviewed by researchers to assess eligibility, to have the trial fully explained and answer any questions from the participant. If eligible, fully informed and consenting they will be entered into the study and randomisation.

7.4 Retention of study documentation

Paper copies of the relevant trial documentation from the study will be held for a period of nine years at the University of Exeter whilst electronic copies will be held for the duration advised by the relevant NHS ethics committee.

8.0 Service User Involvement

The COBRA team work closely with national consumer organizations including RETHINK and Depression Alliance. The chief executive of Depression Alliance (O'Neill) is a full applicant on this proposal and has advised the applicant team throughout. All sites have excellent local patient and public involvement (PPI) mechanisms. For COBRA, this will be led from the Mood Disorders Centre via our 'Lived Experience Group' – 20 people with personal experience of depression and its treatment. All Trial Management Group meetings will be attended by O'Neill and at least one member of the Lived Experience Group. Selection and writing of participant materials (trial information leaflets and consent forms; clinical materials; training materials) will be edited by this group, standard practice in our trials. We will follow national good practice guidance for researchers on public involvement in research and the paying of service users actively involved in research. We will also work with our service user representatives to ensure that our dissemination strategies are inclusive and accessible to other people who use services.

9.0 Research Governance

The trial will be conducted to protect the human rights and dignity of the participant as reflected in the 1996 version of the Helsinki Declaration.
Patients will not receive any financial inducement to participate. In order to protect the trial participants the following provisions will be made/upheld; the trial has been designed to minimise pain, discomfort and fear and any foreseeable risk in relation to the treatments involved; the explicit wishes of the participant will be respected including the right to withdraw from the trial at any time; the interest of the patient will prevail over those of science and society; provision will be made for indemnity by the investigator and sponsor. The study has full approval from all regulatory bodies, Research Ethics Committee etc.

9.1 Monitoring and adverse events

All serious adverse events that are treatment related will be recorded and immediately reported to the Data Monitoring and Ethics Committee (DMEC), trial sponsor and NRES ethics committee except those that the protocol identifies as not requiring immediate reporting. The immediate report will be followed up by a detailed, written report and further information if requested. Inherent in the nature of the population under scrutiny is the risk of suicide. We will follow good clinical practice in monitoring for suicide risk during all encounters with trial participants. Where any risk to participants due to expressed thoughts of suicide is encountered, we will report these directly to the GP (with the participant's expressed permission) or if an acute risk is present will seek advice from the general

practitioner immediately and/or follow locally established suicide management plans. Fatal or serious life-threatening events will be recorded and reported to the Trial Steering Committee (TSC) and Research Ethics Committee within seven days of knowledge of such cases. All other suspected serious unexpected adverse events will be reported to the DMEC, trial sponsor and ethics committee within 15 days of first knowledge.

A TSC will be set up and will include an independent chair, an academic GP and at least two other independent members, along with the lead investigator and some other study collaborators. The TSC will meet at least once a year.

A DMEC committee will be set up and will comprise an independent mental health statistician and clinician. The role of the DMEC is to review serious adverse events thought to be treatment related and look at outcome data regularly during data collection.

9.2 Suicide and self-harm

Inherent in the nature of the population under scrutiny is the risk of suicide. We will follow good clinical practice in monitoring for suicide risk during all encounters with trial participants. Where any risk to participants due to expressed thoughts of suicide is encountered, we will report these directly to the GP (with the participant's expressed permission), or if an acute risk is present we will seek advice from the general practitioner immediately and/or follow locally established suicide management plans.
Fatal or serious life-threatening events will be recorded and reported to the Trial Steering Committee and Research Ethics Committee within seven days of knowledge of such cases.
All other suspected serious unexpected adverse events will be reported to the DMEC, trial sponsor and Research Ethics Committee within 15 days of first knowledge.

10.0 Trial Management

10.1 Sponsorship

The University of Exeter will act as a sponsor for the COBRA Trial.

Sponsor Representative:

Dr Michael Wykes
Policy, Impact and Performance Manager
Research & Knowledge Transfer
University of Exeter
Email: m.c.wykes@exeter.ac.uk
T: +44 (0)1392 722351
M: +44 (0)7799 656261

Research & Knowledge Transfer is ISO 9001:2008 accredited
Sponsor Reference for the COBRA trial: 88135

10.2 Indemnity

Responsibility for indemnity covering participants is covered by the respective authorisations provided at each site, these are:
University of Exeter

Devon Partnership Trust
University of York
Leeds Community Healthcare NHS Trust
Tees, Esk and Wear Valleys NHS Foundation Trust

10.3 Funding

Research funding has been secured from the National Institute of Health Research – Health Technology Assessment programme
(Reference No: 10/50/14).

10.4 Trial Steering Committee (TSC)

A TSC will be set up and will include an independent chair, an academic GP and at least two other independent members, along with the lead investigator and some other study collaborators. The TSC will meet at least once a year.

10.5 Data Monitoring and Ethics Committee (DMEC)

DMEC committee will be set up and will comprise an independent mental health statistician and clinician. The role of the DMEC is to review serious adverse events thought to be treatment related and look at outcome data regularly during data collection.

10.6 Recruiting centres

There will be three recruiting centres, the lead site is in Exeter with two collaborating centres (Durham and Leeds) each will be co-ordinating the recruitment of participants to the study at their site. Each study centre will utilise one or more primary care trusts for recruitment via GP surgeries as Patient Identification Centres.

10.7 Day-to-day management of the trial

The chief investigator (Professor David A Richards) will be in charge of the overall management of the trial. The Exeter-based Trial Manager will be responsible for the co-ordination of the study between the three sites in Devon, Durham and Leeds. An associate research fellow and trial administrator will carry out the day-to-day activities involved in running the trial at each site. Delivery of the randomised therapy will be carried out by trained therapists at each site. An Associate Research Fellow will be responsible for the qualitative components of the study.

A local trial management group will be formed at each study centre and regular meetings will be held.

10.8 Responsibilities of the applicants

There will be a Principal Investigator at each of three sites:

David Richards will act as the Chief Investigator with overall responsibility for the study and also act as mental health specialist and lead for qualitative research.
Dr David Ekers (Durham): Responsible for the local running of the trial in Durham site and the provision of methodological input. Was lead researcher on Phase II pilot trial.

Dr Dean McMillan (Leeds): Responsible for the local running of the trial at the Leeds site and the provision of methodological input. Will be contributing to fidelity of behavioural and cognitive-behavioural treatments

In addition the lead principal investigators Dean McMillan, David Ekers, and David Richards, will provide input in delivery and training of BA to generic workers for the behavioural activation aspects of the study.

Professor Simon Gilbody: trial design and primary care mental health expertise
Prof Rod Taylor: trial statistician
Dr Sarah Byford: trial health economist
Ms Emer O'Neill: advice on Public and Patient Involvement in Depression Services, assisted by the Lived Experience Group at the Mood Disorders Centre, University of Exeter.
Professor Willem Kuyken: trial design, cognitive therapy expertise, process evaluation
Professor Ed Watkins: trial design, development and supervision of BA
Dr Kim Wright: trial design and clinical education
Dr Heather O'Mahen: BA expertise and clinical education
Dr Paul Farrand: BA expertise, CBT expertise and clinical education

We have engaged the independent consultancy services of UK (Oxford Cognitive Therapy Centre) and international experts (Hollon, Dimidjian, Martell) in BA and CBT to advise on training and supervision and to independently validate clinicians' fidelity to BA and CBT. Dr Tim Burke, Chair of the North Devon GP Commissioning Consortia and lead GP for mental health in Devon will provide GP input to the trial.

10.9 Dissemination

We will follow established practice in our centre in disseminating the results of the COBRA trial using the widest range possible of peer reviewed scientific journals and professional publications. We will present at conferences both national and international. Results will be incorporated into our clinical training programmes and we will make recommendations to regulatory bodies such as NICE and the British Psychological Society and the Royal Colleges of Psychiatry and Nursing. We will provide a brief report for participants to be available via GP surgery.

11.0 References

1. Murray CJ, Lopez AD. *The global burden of disease: a comprehensive assessment of mortality and disability from disease, injuries and risk factors in 1990*. Boston Mass: Harvard School of Public Health on behalf of the World Bank, 1996.
2. Kessler RC, Berglund P, Demler O, *et al*. The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 2003; 289: 3095-3105.
3. Singleton N, Bumpstead R, O'Brien M*, et al*. *Psychiatric morbidity among adults living in private households, 2000*. London: The Stationary Office. 2001.

4. Andrews G, Henderson S, Hall W. Prevalence, comorbidity, disability and service utilisation: overview of the Australian Mental Health Survey. *British Journal of Psychiatry* 2001; 178: 145-153.
5. Keller MB. Long-term treatment of recurrent and chronic depression. *Journal of Clinical Psychiatry* 2001; 62(supplement 24): 3-5.
6. Centre for Economic Performance. *The Depression Report: A New Deal for Depression and Anxiety Disorders.* London: London School of Economics and Political Science Centre for Economic Performance, 2006.
7. National Institute for Health and Clinical Excellence. *Depression: Management of depression in primary and secondary care.* National Institute for Health and Clinical Excellence, 2009.
8. Bird A. *We need to talk: the case for psychological therapy on the NHS*. Mental Health Foundation, 2006.
9. DeRubeis RJ, Hollon SD, Amsterdam JD, *et al*. Cognitive therapy vs. medications in the treatment of moderate to severe depression. *Archives of General Psychiatry* 2005; 62: 409-416.
10. Rush AJ, Fava M, Wisniewski SR, *et al*. Sequenced treatment alternatives to relieve depression (STAR*D): Rationale and design. *Controlled Clinical Trials* 2004; 25: 119-142.
11. Web link http://www.iapt.nhs.uk/
12. Hollon SD, Muñoz RF, Barlow DH, *et al*. Psychosocial intervention development for the prevention and treatment of depression: Promoting innovation and increasing access. *Biological Psychiatry* 2002; 52: 610-630.
13. Ferster CB. A functional analysis of depression. *American Psychologist* 1973; 28: 857-870.
14. Lewinsohn PM. A behavioral approach to depression. In RM Friedman, MM Katz (Eds.), *The psychology of depression: Contemporary theory and research* (p. 157-185). Wiley, 1974.
15. Jacobson NS, Martell CR, Dimidjian S. Behavioral activation treatment for depression: Returning to contextual roots. *Clinical Psychology: Science and Practice* 2001; 8: 255-270.
16. Martell CR, Addis ME, Jacobson NS. *Depression in context: Strategies for guided action*. Norton and Co, 2001.
17. Addis E, Martell CR. Overcoming depression one step at a time. New Harbinger, 2004.
18. Beck AT, Rush AJ, Shaw BF, Emery G. *Cognitive therapy of depression: A treatment manual.* Guilford Press, 1979.

19. Kuyken W, Tsivrikos D. Therapist Competence, Comorbidity and Cognitive-Behavioral Therapy for Depression. *Psychotherapy and Psychosomatics* 2009; 78: 42-48.
20. Ekers D, Richards D, Gilbody S. A Meta Analysis of Randomized Trials of Behavioural Treatment of Depression. *Psychological Medicine* 2008; 38: 611-623.
21. Ekers D, Richards DA, McMillan D, Bland JM, Gilbody S. Behavioural Activation delivered by the non specialist: phase II randomised controlled trial. *British Journal of Psychiatry* 2011; 198: 66-72.
22. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *Journal of General Internal Medicine* 2001, 16(Supplement 9):606-613.
23. Jones B, Jarvis P, Lewis J, Ebbutt A. Trials to assess equivalence: the importance of rigorous methods: *Br Med Journal* 1996; 313: 36-39,
24. Piaggio G, Elbourne D, Altman D, Pocock S, Evans S. Reporting of Noninferiority and Equivalence Randomized Trials An Extension of the CONSORT Statement: *Am Med Assoc*, 2006; 295: 1152-1160.
25. National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. NICE, 2008.
26. McCrone P, Dhanasiri S, Patel A, et al. *Paying the Price: The Cost of Mental Health Care in England to 2026*. King's Fund, 2008
27. Medical Research Council. *Developing and Evaluating Complex Interventions: New Guidance*. MRC; 2008.
28. Dimidjian S, Hollon S, Dobson K, *et al*. Randomized trial of behavioural activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. *J Consult Clin Psychol* 2006; 74: 658–70.
29. Watkins ER, Scott J, Wingrove J, et al. Rumination-focused Cognitive Behaviour Therapy for Residual Depression: a case series. *Behaviour Research and Therapy* 2007; 45: 2144-2154
30. Watkins ER. Depressive rumination: Investigating mechanisms to improve cognitive-behavioral treatments. *Cognitive Behaviour Therapy* 2009; 38: 1, 8-14.
31. Beck J. *Cognitive therapy: Basics and beyond.* Guilford Press, 1995.
32. Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I : History, rationale, and description. *Archives of General Psychiatry* 1992; 49: 624–629.
33. Löwe B, Unützer J, Callahan CM, *et al*. Monitoring depression treatment outcomes with the PHQ-9. *Med Care* 2004; 42:1194-1201.
34. Snapinn SM. Noninferiority trials *Curr Control Trials Cardiovasc Med* 2000; 1: 19–21.
35. EMEA Committee For Medicinal Products For Human Use (CHMP). Guideline on the choice of the non-inferiority margin. European Medicines Agency, 2005.

36. Kuyken W, Byford S, Taylor RS, Watkins E, *et al*. Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. *J Consult Clin Psychol 2008; 76:* 966-978.
37. Baldwin S, Murray D, Shadish W, et al. Intraclass Correlation associated with therapists: estimates and applications in planning psychotherapy research. *Cognitive Behaviour Therapy;* in press.
38. Watson JM, Torgerson DJ: Increasing recruitment to randomised trials: a review of randomised controlled trials. *BMC Medical Research Methodology* 2006, 6: 34.
39. Richards DA, Hughes-Morley A, Hayes RA, *et al*. Collaborative Depression Trial (CADET): multi-centre randomised controlled trial of collaborative care for depression - study protocol. *BMC Health Services Research* 2009; 9:188.
40. Kuyken W, Byford S, Byng R, *et al*. Study protocol for a randomized controlled trial comparing mindfulness-based cognitive therapy with maintenance anti-depressant treatment in the prevention of depressive relapse/recurrence: the PREVENT trial. *Trials 2010; 11.*
41. Gilbody S, Richards D, Barkham M. Diagnosing depression in primary care using self-completed instruments: a UK validation of the PHQ9 and CORE-OM. *British Journal of General Practice* 2007; 57: 650-652.
42. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 Health Survey: Manual and Interpretation Guide. The Health Institute, New England Medical Centre, 1993.
43. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy* 1990; 16(3):199–208.
44. Bower P, Byford S, Sibbald B, *et al* Randomised controlled trial of non-directive counselling, cognitive – behavioural therapy, and usual general practitioner care for patients with depression. II: Cost-effectiveness. *BMJ* 2000; 321: 1389 -1392.
45. Kessler RC, Barber C, Beck A. The World Health Organization Health and Work Performance Questionnaire (HPQ). *Journal of Occupational & Environmental Medicine* 2003; 45: 156-174.
46. Drummond M F, O'Brien B, Stoddart GL. *Methods for the Evaluation of Health Care Programmes.* Oxford University Press 1997
47. Curtis L. *Unit Costs of Health and Social Care*. PSSRU, 2010.
48. British Medical Association and the Royal Pharmaceutical Society. *British National Formulary*. 2010.
49. Kraemer HC, Wilson GT, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. *Archives of General Psychiatry* 2002; 59: 877-883.
50. Strunk DR, DeRubeis RJ, Chiu AW & Alvarez J. Patients' Competence in and Performance of Cognitive Therapy Skills: Relation to the Reduction of Relapse Risk

Following Treatment for Depression. *Journal of Consulting and Clinical Psychology* 2007; 75: 523-530.

51. Bosmans JE, de Bruijne MC, van Hout HPJ, Hermens MLM, Adèr HJ, van Tulder MW. Practical Guidelines for economic evaluations alongside equivalence trials. *Value in Health* 2008; 11: 251-258.
52. Efron B, Tibshirani R J. *An introduction to the bootstrap*. Chapman & Hall, 1993.
53. Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. *Stat Med* 2000; 19: 3219-36.
54. Briggs AH, O'Brien B. The Death of Cost-minimisation Analysis? *Health Economics* 2001; 10: 179-184.
55. Stinnett A. Mullahy J. Net Health Benefits: A New Framework for the Analysis of Uncertainty in Cost-Effectiveness Analysis. *Medical Decision Making* 1998; 18: S68-S80.
56. Van Hout BA, Al MJ, Gordon GS, *et al* Costs, effects and C/E-ratios alongside a clinical trial. *Health Economics* 1994; 3: 309-319.
57. Fenwick E, Byford S. A guide to cost-effectiveness acceptability curves. *British Journal of Psychiatry* 2005; 187: 106-108.
58. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Economics* 2001; 10: 779 -787.
59. Claxton K**.** Bayesian approaches to the value of information: implications for the regulation of new care technologies. *Health Economics* 1999; 8:269-74.
60. Driessen E, Hollon SD. Cognitive behavioral therapy for mood disorders: efficacy, moderators and mediators*. Psychiatr Clin North Am*. 2010; 33: 537-55.
61. Kuyken W, Watkins E, Holden E, *et al***.** How does mindfulness-based cognitive therapy work?. *Behav Res Ther* 2010; *48:* 1105-1112.
62. Emsley R, Dunn G. Mediation and moderation of treatment effects in randomised controlled trials of complex interventions. *Statistical Methods in Medical Research* 2010; 19: 237–270
63. Kanter J, Mulick P, Busch Am, Berlin KS, Martell C. The Behavioral Activation for Depression Scale: Psychometric properties and Factor structure. *Journal of Psychopathology and Behavior Assessment* 2007; 29: 191-202.
64. Weissman AN, Beck AT. Development and validation of the dysfunctional attitude scale. Paper presented at the Annual meeting of the Association for the Advanced Behavior Therapy, Chicago, November 1978. Available at: http://www.eric.ed.gov/
65. Pope C, Ziebalnd S, Mays N. Qualitative research in health care: analysing qualitative data. BMJ 2000;320:114–6.
66. Richards, DA, Lankshear, AJ, Fletcher, *et al*. Developing a UK Protocol for Collaborative Care: A Qualitative Study. *General Hospital Psychiatry* 2006; 28: 296-305.

67. Miles MB, Huberman AM. Qualitative data analysis: an expanded sourcebook. Sage, 1994.

Appendix 1: Study Timeline

COBRA - RCT	**Months**								
Activity	- 6-0	1-6	7-12	13-18	19-24	25-32	33-38	39-44	45-48
ethics and R & D approvals									
recruit trial manager									
research team recruitment									
clinician recruitment									
trial protocol submission for publication									
complete training materials and clinical protocols									
GP practice recruitment									
training of clinicians									
participant recruitment									
6 month follow-ups									
12 month follow-ups									
18 month follow-ups									
primary clinical analysis									
process analysis									
12 month analysis									
18 month analysis									
economic analysis									
write up and dissemination									

Appendix 2: Study Flow Chart