A long-term follow-up of the CoBalT study participants

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1. Background

Depression is a major contributor to the global burden of disease (1) and the costs to the NHS are considerable. The costs of services for depression have been estimated at £1.7 billion and the annual cost to the NHS is £2085 per patient (2). Lost productivity due to depression has been estimated to cost society £5.8 billion (2). Therefore, effective interventions have the potential to substantially reduce the economic cost of this condition (to the NHS, patients and society).

Non-response to antidepressant medication is known to be a substantial problem in primary care. It has been estimated that only around one-third of those prescribed antidepressants will experience remission of symptoms (3). Those individuals who continue to have significant depressive symptoms following treatment with an adequate dose and duration of antidepressant medication are often referred to as having treatment resistant depression. Increasing the evidence base on effective 'next step' treatments is essential in order to improve outcomes for the large number of patients whose symptoms do not improve following treatment with medication.

Patients often indicate a preference for talking therapies and depression guidelines advocate increased use of cognitive behavioural therapy (CBT) (4). However, despite expansions in psychological services as a result of the Improving Access to Psychological Therapies project (IAPT) (5, 6) in England and similar projects in Scotland, CBT is still a limited resource, often reserved for those who have not responded to antidepressants. Until recently, there was no high quality evidence from large-scale randomised controlled trials (RCTs) regarding the effectiveness of CBT as a 'next-step' option for patients whose depression had not responded to treatment with antidepressants.

1.1 Findings from the CoBalT trial

The CoBalT trial examined the clinical and cost-effectiveness of CBT as an adjunct to usual care that included pharmacotherapy for patients whose depression had not responded to treatment with antidepressant medication alone. In total, 469 patients were randomised to either continue with usual care or receive CBT in addition to usual care. Ninety percent (n = 422) of participants were followed-up at 6 months (the time point of the primary outcome) and 84% (n = 396) at 12 months. We found that CBT in addition to usual care was effective at reducing depressive symptoms. Ninety-five participants (46.1%) in the intervention group met criteria for 'response' (at least a 50% reduction in depressive symptoms compared to baseline) at 6 months compared to 46 participants (21.6%) in the usual care group (odds ratio (OR): 3.26 (95%CI: 2.10, 5.06) $p<0.001$). Those randomised to the intervention group were more likely to experience 'remission' (Beck Depression Inventory (BDI-II) score<10) at 6 months (OR: 2.30 (95%CI: 1.39, 3.81) $p=0.001$). Those randomised to receive the intervention also reported improvements in quality of life. Importantly, these effects were maintained over the 12 month follow-up period. These results have been recently published in The Lancet (7).

The economic evaluation concluded that CBT as an adjunct to usual care was cost-effective in this patient group over a period of 12 months. From the perspective of the health care provider the incremental cost-effectiveness ratio was £14,911 per QALY gained. The net monetary benefit (NMB) at the threshold of £20,000 per QALY was £289 (95% CI: -£603 to £1182) and the probability that the intervention was cost-effective at this level was 0.74.

1.2 The need for long-term outcome data

Whilst these results are encouraging, there is currently no data on the long-term clinical and cost-effectiveness of such an intervention. The question remains as to whether the beneficial effects of the intervention observed at 12 months are maintained over subsequent years or whether such effects 'wear off'.

Given the educational approach that underpins CBT, it has the potential to produce a more sustainable improvement than other treatments (which will largely comprise pharmacotherapy). Several authors have called for more research into the long-term outcomes of CBT (8, 9) and, in particular, have highlighted the need for evidence with regards to long-term cost-effectiveness (8).

Currently, there is little robust evidence for the effectiveness of CBT over the long-term. Many RCTs of CBT interventions report outcomes after just 12-16 weeks (10, 11), although some include a longer follow-up (10-16 months (12-16)). Others have only followed up a select group of trial participants, for example, 'responders' to CBT (17).

There are some indications that CBT may be effective over the long-term (3-4 years), but this evidence mainly relates to the role of CBT in relapse prevention (18) and includes small studies (n = 40) (19) that were underpowered to detect a clinically important difference between groups. In a larger RCT, 158 patients with residual depressive symptoms recruited from outpatient clinics were randomised to either continue with antidepressant medication as part of their clinical management or to receive 16 sessions of CBT over 20 weeks in addition (16). After 68 weeks (~1.3 years), the relapse rate was significantly reduced (29%) amongst those who received CBT compared with usual care (47%) (adjusted hazard ratio for relapse: 0.51 (95%CI: 0.32, 0.93)) (16). Eighty-five percent of these trial participants (n = 135 out of 158) were followed up over the long-term, on average 6 years after randomisation (20). The difference between groups was only lost fully after approximately 4 years (actuarial recurrence rates at 3.3 yrs: CBT 41%; usual care 49%; and at 4.3 yrs: CBT 56%, usual care: 55%) (20).

Data on long-term cost effectiveness are sparse. In the Paykel trial of CBT for residual depression (16), data on resource utilisation were collected. Over 68 weeks, CBT was found to be more effective but more costly than usual clinical management (21). The cost per relapse prevented was £4328 equating to approximately £12.50 per relapse-free day (21). However, no data on quality adjusted life years (QALYs) were collected. Therefore, it is not possible to determine cost-effectiveness according to the threshold of £20,000-£30,000 per QALY used by the National Institute for Health and Clinical Excellence (22). Moreover, no data on costs were available for the 6-year follow-up (20).

Other reports on cost-effectiveness of CBT, for example, Durham et al (23) have focussed on different patient populations (those with anxiety disorders or psychosis) and interventions of varying intensity. For example, low intensity interventions for anxiety disorders comprising an average of 4 sessions and less than 3 hours contact time. Whilst the findings from this latter study (restricted to RCTs conducted in Scotland) (23) also supports the view that patients who receive CBT are more likely to have a better long-term outcome, the effects diminished over time and there was little evidence that CBT was cost-effective. However, attrition was high (only 46% of the trial participants were followed-up) and differences in the patient populations and interventions mean that these findings cannot be generalised to the population of patients with TRD studied in CoBalT.

1.3 Summary

Given that, within the NHS, CBT is often reserved for non-responders to antidepressants, it is both important and timely to evaluate the long-term clinical and cost-effectiveness of such a strategy. A one-off postal follow-up of the CoBalT study participants therefore provides a unique and highly efficient opportunity to gather information that would be of direct relevance to clinicians and policymakers.

2. Research Objectives

This research study has two main objectives. Amongst primary care patients with treatment resistant depression: (i) is CBT (in addition to usual care that includes pharmacotherapy) effective in reducing depressive symptoms and improving quality of life over the long-term (approximately 4 yrs), compared with usual care alone?; (ii) is this strategy cost-effective?

In addition, a nested qualitative study will be conducted with those who completed the long-term follow-up study questionnaire in order to explore how patients from both arms of the trial continued to manage their depression over the long-term (since the 12 month follow-up). Amongst those who received CBT during the trial, the study will also explore the extent to which they have continued to use the techniques learnt and to incorporate CBT strategies into their lives.

3. Research Methods

3.1 Study Design

This is a long-term follow up of patients who were originally recruited to a randomised controlled trial (acronym: CoBalT).

3.2 Setting and Infrastructure

Participants in the original CoBalT trial were recruited from 73 general practices across three study sites (Bristol, Exeter and Glasgow).

This follow-up study will be co-ordinated from the University of Bristol. In order to maximise the success of the project, we will apply for continued support from the Mental Health Research Network (MHRN).

3.3 Study Participants

Eligible patients are those who: (i) gave consent to be randomised into the CoBalT trial; (ii) had not withdrawn from the study; and (iii) have already provided written informed consent indicating that they are willing to be contacted about future depression studies. This comprises 430 potential participants out of the 469 individuals who took part in the CoBalT trial (intervention group: n = 213; usual care group: n = 217).

3.4 Data collection

3.4.1 Stage 1 – Contacting GP practices

Whilst the patients have already provided written informed consent to be re-contacted by the research team, we will write to all GP practices that took part in the CoBalT study to inform them that this follow-up study is taking place (GP_CoverLetter_v1.doc). This will be accompanied by a GP information leaflet about the study (GP_InfoLeaflet_v1.doc).

The purpose of this contact is two-fold.

Firstly, to ensure that the practices are aware that the study is taking place. Although no intervention is planned, issues relating to patient safety may arise during the course of re-contacting participants. It will therefore be important that GPs are aware of the research in the event that a member of the research team needs to contact a member of practice staff to inform them of any concerns about harm to the individual or others.

Secondly, it is important to ensure that no inappropriate invitation letters are sent out. Therefore, the initial letter to the practice informing them that the follow-up study is taking place will be followed by a telephone call to the practice to ask them to check the list of potential participants from the CoBalT database against the practice records, in order to avoid any inappropriate follow-up

invitations being sent out (e.g. to patients who might have died), and to ensure letters are not posted to an address at which the patient is no longer living. GP practices will be asked to provide up-to-date address details, if applicable. Those participants for whom the GP practice decides that it would be inappropriate for the research team to re-contact will be excluded from the study.

The research team will offer to visit the practice to discuss the study in more detail, if requested by the practice.

3.4.2 Stage 2 – Mailing of postal questionnaire to potential participants

Once the list of potential participants has been reviewed by the GP practices, the participants will be mailed a study questionnaire. A covering letter and information leaflet sent with the questionnaire will explain the purpose of the follow-up study and give contact details of the research team in case the individual has any questions about the study or taking part (PT_CoverLetter_v1.doc/PT_InfoLeaflet_v1.doc). As in the original study, a self-report questionnaire will be used in order to eliminate the possibility of observer bias. Mailings will be staggered over six months to ensure a steady workload for the researcher.

The questionnaire will be similar to those that the participant completed as part of the original study. It will take approximately 30 – 40 minutes to complete. Further details of the content of the questionnaire are given in section 3.5 (outcome measures).

In the questionnaire, patients will be asked for their consent for the study team to pass on summary information regarding their depressive symptoms to their GP (Consents_v1/ GPFeedback_v1). This information may be useful to their GP in the management of their depression.

Patients will also be asked for consent for the research team to access their medical records (Consents_v1) in order to gather information on the number of consultations in primary care and details of all antidepressant medication prescribed (name, dose and number of prescriptions) since the 12-month follow-up. This will enable a validation study to be carried out comparing the number of consultations in primary care in the past 6 months and antidepressant medication prescribed, as reported by the participant in their questionnaire, with data obtained from primary care medical records. This validation study will be conducted on a random sample of 50 participants who return a postal questionnaire and who provide consent for the research team to have access to their medical records. Data on consultations and antidepressant prescriptions since the 12 month follow-up will also be needed for explanatory purposes aiding the interpretation of any differences (or lack of a difference) in depression outcomes between the two groups at the long-term follow-up.

Patients who are willing to participate in the follow-up study will be asked to complete the questionnaire booklet and post it back to the research team in the pre-paid envelope. Written consent will not be obtained. Rather, completion of the questionnaire will be taken as indication of consent to participate.

Those who decide they do not wish to participate will be asked to return the uncompleted questionnaire. Individuals who return a blank questionnaire will not be contacted further.

A reminder mailing will be sent to all those who have not responded after 2 weeks. In the event of continued non-response, participants will be contacted by telephone (using existing contact details) and they will be asked to complete a brief questionnaire over the telephone. The content of this brief questionnaire will be modelled on the questionnaire administered over the telephone in the previous study that collected data on depressive symptoms using the PHQ-9, use of medication and other treatments received.

3.4.3 Tracing patients whose address has changed

It is possible that in the 2 – 3 years since their last contact by the CoBalT study team, some of the participants will have moved. The vital status of those individuals who cannot be contacted using existing contact details will be ascertained via the NHS Central Register (for England: www.ic.nhs.uk/services/medical-research-information-service; or Scotland: www.groscotland.gov.uk/national-health-service-central- register/index.html). The consent to re-contact specified that "….*if I have moved you will use the NHS Central Register to obtain my new address*" and hence, based on the experience of other researchers using these registers, we anticipate being able to obtain an up-to-date address directly from the relevant PCT/Health Board. If the PCT/Health Board declines to pass on such information directly to the research team, then the research team would write to the relevant PCT/Health Board Administrator requesting that an information leaflet and invitation letter about the follow-up study is forwarded to the patient's GP who will, in turn, be asked to forward the information about the study to the individual concerned. Once contact with the individual was established, the procedure for follow-up and obtaining outcome data would follow that outlined above.

3.5 Outcome Measures

The follow-up questionnaire will include the outcomes measured as part of the 6- and 12-month trial follow-up assessments, to enable direct comparisons to be drawn with this long-term follow-up data.

Primary Outcome

The primary outcome will be a self-report measure of depressive symptoms, the Beck Depression Inventory (BDI-II) score (24), at the time of this follow-up (approximately 4 years post-randomisation).

Secondary Outcomes

Secondary outcomes will include quality of life (assessed using the SF-12 (25)) a widely used scale that primarily concerns functional status. As in the main trial, patients will also be asked to complete additional measures of depression (PHQ-9 (26)) and anxiety (GAD-7 (27)) in order to enable comparison with data from psychological services (IAPT) and the EQ-5D-5L (28) for the estimation of Quality Adjusted Life Years (QALYs).

Participants will also be asked about whether they are taking antidepressant medication and for details of the name and dose of medication, duration of treatment, and about their adherence to such medication over the previous six weeks. Details of other co-morbidities will be ascertained using a question from the National GP Patient Survey (http://www.gp-patient.co.uk/).

Data on health care utilisation for the economic evaluation will be collected using a postal questionnaire. This will include questions about primary and secondary care and private treatments accessed to treat depression. As with the trial, the analysis will include all primary care contacts irrespective of reason for encounter but data on secondary care will be restricted to contacts related to mental health problems; this will include outpatient appointments, community mental health team contacts and details of any in-patient stays. Participants will also be asked for details of any computerised CBT or psychological therapies accessed (in the NHS, voluntary sector or privately) since the 12 month follow-up.

Additional detail about health care utilisation will be collected by telephone for those individuals who endorse items in the postal questionnaire. Participants will be asked to provide details of their telephone number (and the best times to contact them) for this purpose. This telephone call will take approximately 10-15 minutes.

3.6 Payment to participants

As a sign of our appreciation for all the help participants give, we will send a £10 gift voucher to all participants who complete the follow-up questionnaire. This gift voucher will be sent from the coordinating centre (Bristol) on receipt of the completed questionnaire.

3.7 Anticipated follow-up rates and precision around differences between groups at 4 years

The fact that this is a long-term follow-up of participants in a trial means that an *a priori* power-based sample size calculation is not appropriate. Instead, therefore, we have set out below the likely precision around differences in outcomes (both in terms of clinical outcomes and measures of cost-effectiveness) that would be obtained based on a range of follow-up rates.

Precision around differences in clinical outcomes

Whilst the primary outcome for the trial was a binary variable of 'response' (defined as at least a 50% reduction in depressive symptoms on the BDI relative to baseline), for this longer term follow-up, we will specify the clinical outcome of interest as the difference in mean BDI scores at this time point. Use of a continuous outcome will maximise power and thus provide the most precise estimate of the difference between groups.

The precision around such a difference will depend upon the final follow-up rate achieved. Follow-up rates in CoBalT were high, and there was no evidence of differential attrition between arms (84% of both groups followed up at 12 months). This long-term follow-up will attempt to re-contact all 430 participants who have not withdrawn from the study and who gave consent to be re-contacted. Of these 430 individuals, 396 provided data at 12 months post-randomisation. The table below provides details of the margin of error around the difference in mean BDI scores between groups at 4 years for a range of values for the follow-up rate (Table 1).

Table 1 – Precision around difference in mean BDI scores at 4 years based on varying assumptions regarding the likely follow-up rate

Number to be contacted	430	430	430	430
Follow-up rate at 4-years*	**50%**	**55%**	**60%**	**65%**
Follow-up rate as % of those contacted at 12 mths	*54%*	*60%*	*65%*	*71%*
Number that will be followed up at 4 years	215	237	258	280
Margin of error around difference in mean BDI between the trial arms (in units of SD)	± 0.268	± 0.255	± 0.244	± 0.234
Margin of error expressed in terms of BDI points (using SD at 12 months which was 11.9 points)	± 3.2	± 3.0	± 2.9	± 2.8
Increase in imprecision of estimate relative to precision at 12 months	36.0%	29.4%	23.9%	18.8%

**contacted and completed follow-up questionnaire (by post or telephone)*

In the table above, the follow-up rate at 4-years varies between 50% and 65%, which equates to 54% to 71% of those who were contacted at 12-months. Whilst 86% (95%CI: 82%, 90%) of those who completed the exit questionnaire for the study would 'consider taking part in other research in the future', we anticipate based on our experience in other trials, that completion rates for a postal

questionnaire are likely to be lower than those obtained for follow-ups conducted face-to-face. Therefore, we believe that the estimated range for the likely follow-up rate, and hence the estimates of precision, are realistic.

At 12 months, the margin of error around a difference of 5 points on the BDI was 0.197 SD, equating to 2.3 points on the BDI. Assuming a follow-up rate of 50-65% at 4 years, the margin of error would increase to 0.234-0.268 SD, equating to 2.8-3.2 points on the BDI, representing an increase in the margin of error of 18.8%-36.0% compared to that observed at 12 months. However, the primary comparisons for the clinical outcome data would utilise repeated measures analyses (see statistical analysis section), with an associated increase in precision. Only through the use of face-to-face follow-ups would it be possible to increase the follow-up rate and hence reduce the margin of error, but such an approach would substantially increase the cost of the proposed extension.

Precision around estimates of cost-effectiveness
In terms of the likely precision of estimates calculated as part of the economic analyses, in the table below, we present estimates of the precision around the net monetary benefit (NMB) for sample sizes based on the lower (50%) and upper (65%) limits of the follow-up rates given previously. The estimates of NMB were produced by simulation, using the results at 12 months and making a number of assumptions regarding the costs and QALYs over the follow-up period. The estimates of precision were achieved by bootstrapping the 4-year estimates of cost and QALYs. The assumptions underpinning the projections were that: (1) the usual care group remain the same in terms of costs and QALYs over the 4 years; (2) the intervention group incur a small increase in primary care costs during years 2 & 3, to bring them in line with usual care, secondary care costs decrease during years 2 & 3 to bring them in line with usual care, and there is a gradual reduction in QALYS, again to bring them in line with usual care over years 2-4; and (3) both groups continue with antidepressant medication as over the 12 months of the trial. These were based on the premise that there may be a decrease in terms of clinical effectiveness over time, and that the resource utilisation in both groups would be likely to become more similar over the course of follow-up (with resource use in the usual care group already having reached a plateau). Costs and QALYs have been discounted at 3.5% per annum.

Notably, there is little difference in the precision of the estimates based on the sample size that would be achieved for the least, and most, optimistic follow-up rates. We can relate the margin of error for the NMB over 4 years, with that obtained for the same statistic at 12 months (NMB at £20,000 per QALY for the reduced set of costs that will form the focus for the 4-year analysis was £77 (95%CI: -£865, £1037)).

Follow-up rate at 4-years	**50%**	**65%**
Follow-up rate as % of those contacted at 12 mths	*54%*	*71%*
Number with complete cost & QALY data at 12mths	*368*	*368*
Number that will be followed up at 4 years	198	260
Net monetary benefit (NMB) where λ = £20K	£1180	£1178
95%CI	(-£3582, £5985)	(-£3113, £5498)

λ = willingness to pay per QALY gain

3.8 Statistical Analysis
Clinical outcomes

The primary clinical outcome will be the BDI score(24) at 4 years post randomisation. We will use repeated measures analyses to compare the groups as randomised, incorporating outcomes at 6 months, 12 months and 4 years (and adjusting for stratification and minimisation variables and baseline measurements of the outcome) to examine whether the treatment effects observed over 12 months are sustained or decline over the long-term. These analyses will use an extension to the method of generalised estimating equations (quasi-least squares: *xtqls* command in Stata) that permits use of a Markov correlation structure to allow for the unequal spacing of measurements(29). This will generate a summary effect measure (regression coefficient) that represents the average difference in mean BDI scores between treatment groups over the 4 years. The assumption that such a summary measure across the four years is appropriate will be tested formally by the introduction of an interaction between treatment group and time.

Secondary analysis
Secondary analyses will also be conducted for the other outcomes measured at 4-years, using repeated measures analyses as described above. In all analyses, we will report regression coefficients (or odds ratios (OR) for binary outcomes) with 95% confidence intervals and p values.

Missing data
The reasons for any missing data within the dataset will be explored and sensitivity analyses will be conducted to examine the impact of missing data on the findings. Under a missing at random assumption, missing data will be imputed using the approach of multiple imputation by chained equation (MICE) (30). If drop-out appears to be informative, we will use methods that simultaneously model the observed data and the missingness process (31) in order to generate unbiased estimates of the difference between groups.

Economic evaluation
The economic evaluation will provide an estimate of cost-effectiveness over the 4-year period. We will use nationally available sources to value the NHS resource use, as described above, to obtain a total cost per patient over the 4-year period. QALYs over the same period will be estimated from the responses to the EQ-5D, adjusted for the mean difference between the groups observed in the main trial. The trial follow-up questionnaires at 6 and 12 months included the earlier version of the EQ-5D (EQ-5D-3L), whilst in this follow-up at ~4 years post-randomisation, we will collect data using the new (more sensitive) version of this instrument (EQ-5D-5L). Therefore, the results of the 'cross walk' exercise (http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html) will be used to map responses on this new version of the EQ-5D (EQ-5D-5L) with responses on the old version of the EQ-5D (EQ-5D-3L) and hence link to the 3L value sets that are needed to permit calculation of QALYs.

Costs and QALYs will be discounted at the rate recommended by NICE (currently 3.5% per annum). The estimates of cost and QALY will be combined to produce an incremental cost-effectiveness ratio and the net monetary benefit (NMB) will be estimated using the threshold willingness to pay of £20,000 to £30,000 per QALY. We will use bootstrapping to obtain a confidence interval around the NMB.

3.9. Qualitative Study

Recruitment and sampling
An invitation letter will be posted to those who completed the full-length version of the follow-up study questionnaire, asking if they would be interested in taking part in a brief telephone interview

about the treatment they have received since the 12 month follow-up, and treatments or other help that they think has been helpful in managing their depression.

An information leaflet about the qualitative study (Pt_InfoLeaflet_LongTerm_QualInterviews_v1) will accompany this invitation letter. Potential participants would also be asked to complete a brief measure of depressive symptoms (PHQ-9) in order to inform the sampling for these interviews. A reminder letter will be sent to those who have not responded after 2 weeks. Those who do not respond to this reminder letter will not be contacted further.

A purposeful sampling strategy will be used to ensure interviews are held with participants from both arms of the trial, from all three centres, and whose recent PHQ-9 score vary in severity. Within this sampling strategy, we will aim for maximum variation in relation to socio-economic background, gender and age. In addition, when sampling individuals from the intervention arm, we will only sample those who received at least 12 sessions of CBT (which is defined as a course of CBT as per the original trial protocol. Interviews will be held with patients over the telephone and should take approximately 20 minutes. Approximately 30-35 interviews will be conducted in total (e.g. 20 intervention and 10-15 usual care), although the final number of patients interviewed will depend on when data saturation is reached.

Data collection
Participants will be interviewed at a time and date that is convenient for them. The interviews will be held by telephone for both pragmatic and methodological reasons; conducting face-to-face interviews across all three sites would be costly in terms of both time and money, and researchers have shown that well planned telephone interviews can gather the same material as those held face-to-face (32, 33). The interviews will be conducted by an experienced qualitative researcher. S/he will secure the participant's verbal consent to take part in an interview immediately prior to starting the interview. With participant consent, the interviews will be audio-recorded and transcribed verbatim. The recordings will be destroyed once the qualitative study is complete.

Data analysis
The interviews will be analysed thematically (34). This approach will entail transcripts being read and re-read by the research team to familiarise themselves with the data, identify emerging themes and to develop a coding frame. Once the coding frame has been agreed, transcripts will be imported into the software package NVivo to allow electronic coding and retrieval of data. Once all the transcripts have been electronically coded, data pertaining to each code will be summarised in tables using an approach based on framework analysis (35).Comparison will then be made within and across the interviews to identify thematic patterns and deviant cases, highlight the views participants hold toward specific issues, e.g. treatments for depression, and to consider whether, for example, participant's experiences of CBT appear to influence the ways in which they manage their depression.

3.10 Production of a short film about CBT

Earlier qualitative interviews with CoBalT participants revealed some of the challenges experienced by individuals receiving CBT, as well as the benefits. It is important that these experiences – both benefits and challenges – are shared widely with patients, GPs who refer people for CBT, and those who commission and provide the service. Therefore, we would like to make a short film where people who have had CBT in the CoBalT study talk about their experience, including the difficulties or challenges of therapy and how they have benefitted. This film would be made available on the internet for the groups mentioned above to access.

An invitation letter (Pt_InvitationLetter_Video_v1) will be sent to all those who completed the full-length version of the follow-up study questionnaire and who had received at least 12 sessions of CBT (which is defined as a course of CBT as per the original trial protocol) to ask if they would be interested in appearing in a short film about CBT. Invitations will only be sent to those recruited by the Bristol site and who are known to be still resident in the local area given the need to travel to a central Bristol location to make the film.

An information leaflet (Pt_InfoLeaflet_CBTvideo_v1) will accompany this invitation letter. A reminder letter (Pt_ReminderLetter_Video_v1) will be sent to those who have not responded after 2 weeks. Those who do not respond to this reminder letter will not be contacted further.

Those who agreed to take part would meet with the research team on two occasions. During the first meeting, which would last about 1.5 hours, we would explain in detail what would be involved. Those who agree to be filmed would be asked to give written informed consent (Pt_VideoConsentForm.doc). Filming would take about 3 hours. We would give participants the opportunity to comment on the film before it was seen by anyone outside the research team in order to ensure that they were happy with the content and presentation.

We would be able to pay reasonable travel expenses, and, as a thank you and in recognition of the participant's time, we would offer a £10 gift voucher.

4. Ethical arrangements including Suicide Policy

Ethical approval and local research governance approvals for the study will be obtained, as appropriate. The study personnel management group and independent Trial Steering Committee will ensure that the study is conducted within appropriate NHS and professional ethical guidelines.

All the information will be kept strictly confidential and held in accordance with the principles of the Data Protection Act. Each participant has an assigned research number and all data are stored without subject name or address. Data will be held on a secure database on a password-protected computer at the University of Bristol. Access to data will be restricted to the research team. In order to enable follow-up contacts, it will be necessary to identify the patients, but access to contact details (e.g. name and address) will be restricted to key members of the research team. Any information about the patient obtained (with their consent) from their medical records will be recorded against research number (anonymised format).

Suicide Policy

As the participants in this study have depression, it is appropriate to have a suicide policy in place. If at any time the researcher believes that there is a significant suicide risk with a patient who is participating in the study, the researcher will ask the patient for their consent to pass this information on to their GP. If the patient refuses for their GP to be notified, the researcher will consult the

appropriate clinician (or nominated deputy) at the research site. This person will examine the patient's data and, if it is considered necessary, will assess the patient. If it is concluded that there is a significant risk, the patient's GP will be notified *without* the patient's consent. However, the nominated clinician would contact the GP without first assessing the patient him/herself if the situation was urgent, again with or without the patient's consent. The need to break confidentiality in situations where there was significant concern about harm to the individual (or others) will be explained in the patient information leaflet.

5. Research Governance and registration framework

The University of Bristol will act as the Sponsor for this study. The University has Clinical Research Insurance to cover the liability of the University to research participants.

In accordance with MRC guidelines, the project will be overseen by a trial steering committee (TSC), which comprises an independent chair, two other independent members and a user representative.

As this study is a follow-up of patients who originally took part in a randomised controlled trial we have contacted the appropriate body (www.controlledtrials.com) and asked for the trial registration information to be amended to include this additional long-term follow-up. In line with current recommendations, relevant trial documentation will be retained for at least 20 years. We anticipate retaining computerised data indefinitely.

6. Project Timetable

This follow-up study has been funded as an extension to the original grant award by the funder NIHR HTA. The funding for this extension period runs from 1st March 2013 to 31st March 2015.

Preparatory work for the study, including obtaining ethics and research governance approval, will take place during the first six months (March – August 2013). During this time, extensions to the study database will take place, and study documentation/questionnaires and standard operating procedures (SOPs)) will be finalised. GP practices will begin to be notified about the follow-up study in July 2013 and data collection is scheduled to begin on 1st September 2013. Contact with participants (by post and, for non-responders, by telephone) and collection of economic data for the validation study will be staggered over a period of 6 months to ensure that the workload was proportionate to the researcher time. Analysis and report writing is scheduled for 6 months, with analysis of the economic data to run alongside the analysis of the clinical outcomes. The qualitative study will begin in September 2014 and will run until the end of March 2015. The process of inviting participants to take part in the short film on CBT will begin in April 2015 and the final film will be completed by the end of September 2015.

Total time: 31 months.

Start of funding: 01/03/2013
Initial contact with GP practices: 01/07/2013
First postal questionnaires to participants: 01/09/2013
Study end date: 30/09/2015

Month	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***	***12***	***13***	***14***	***15***	***16***	***17***	***18***
Study preparation																		
Follow-up recruitment																		

Data cleaning			
Analysis & report writing			
Economic analysis to start			

Month	***19***	***20***	***21***	***22***	***23***	***24***	
Qualitative Study							

7. Expertise

A multidisciplinary research team from 3 centres (Bristol, Exeter and Glasgow), has been assembled with expertise covering RCT design, management & analysis (Wiles, Kuyken, Lewis, Peters); primary care (Kessler, Campbell, Morrison); psychiatry (Lewis, Williams); statistics (Peters); and health economics (Hollinghurst). The qualitative study will be overseen by Dr Katrina Turner, a senior qualitative researcher. The Bristol researchers are based in two buildings within 10 minutes walk on the same University precinct and both Exeter and Glasgow are only just over one and a half hours travelling time by car or plane.

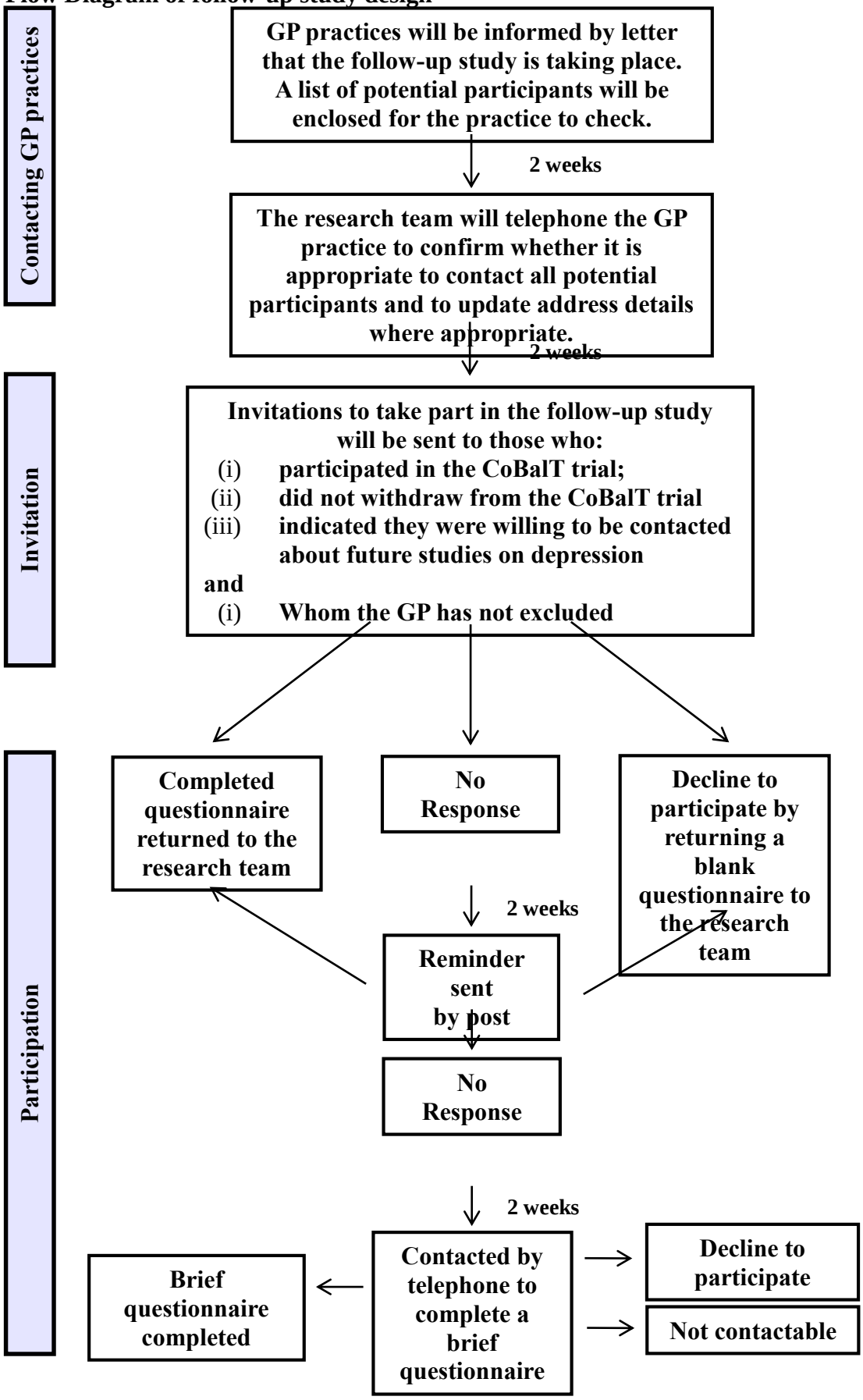
One of the original researchers in Bristol (LT) will be employed to oversee the conduct and running of this follow-up study and would bring with her a wealth of invaluable experience to the project. She would be employed on a part-time basis (0.8FTE) for the duration of the project and would contribute to the analysis and writing up of the final report. She would be supported by a part-time research administrator (0.4FTE for 9 months covering set-up and data collection). We have also budgeted for the support of a Database Manager (6 weeks on an *ad hoc* basis). We would seek adoption by the relevant research network (Mental Health Research Network (MHRN) who would be approached for additional support with recruiting to follow-ups, if necessary.

A management group comprising NW, GL, DK, TP, SH, JC, JM, WK CW and LT will meet monthly by teleconference.

8. Service User input

The West Hub Research Materials Advisory Service (WHRMAS) has provided feedback on the study documentation for participants and amendments to these documents have been made in response to this feedback. A user representative agreed to be a member of the independent Trial Steering Committee that has oversight of the study. This user representative has also agreed to help develop a newsletter providing feedback to participants once the study results are published.

Flow Diagram of follow-up study design



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