Randomised controlled trial of the selective serotonin reuptake inhibitor Sertraline versus Cognitive Behavioural Therapy for anxiety symptoms in people with Generalised Anxiety Disorder who have failed to respond to low intensity psychological interventions as defined by the NICE GAD guidelines

Acronym: ToSCA – Trial of Sertraline versus Cognitive behaviour therapy for generalised Anxiety

OVERALL AIM
Randomised controlled trial (RCT) to compare the clinical effectiveness in terms of symptoms and function of a pharmacological treatment (the SSRI Sertraline) prescribed at therapeutic doses, with a manualised psychological intervention (Cognitive Behavioural Therapy, CBT) delivered by trained psychological therapists to patients with persistent generalised anxiety disorder (GAD) which has not improved with low intensity psychological interventions as defined by NICE.

Hypothesis: Our hypothesis is that in people with Generalised Anxiety Disorder (GAD) who have not responded to low intensity psychological interventions as recommended by NICE, CBT will lead to a greater improvement in their GAD symptoms as measured by the GAD-7 at 12 month follow-up than the protocolised prescription of the SSRI sertraline by the GP.

Primary aim: To assess the clinical effectiveness at 12 months of treatment of the SSRI Sertraline compared to CBT for patients with persistent GAD which has not improved with low intensity psychological interventions

Secondary aim: To calculate the cost-effectiveness at 12 months of the SSRI Sertraline compared to CBT for patients with persistent GAD which has not improved with low intensity psychological interventions.

DETAILED OBJECTIVES:

Internal Pilot

1. To test and refine the recruitment methods for the main trial
2. To ascertain recruitment rates across sites and the acceptability of the overall recruitment process
3. To examine the extent of comorbidity between GAD, depression and other anxiety disorders in the population that is referred into the study
4. To ensure that the intervention can be delivered according to the protocol in both arms, with satisfactory delivery of training and monitoring procedures.
5. To monitor and assess follow-up rates to the completed primary outcome measure (GAD-7) at 3 and 6 months within the pilot trial.

Overall trial

1. To recruit sufficient eligible patients with a DSM IV diagnosis of GAD willing to participate.
2. To compare the effect of high quality reproducible pharmacological and psychological interventions delivered according to clear criteria and evidence based guidelines. We will have a pre-defined algorithm for delivery of the pharmacological intervention and the psychological intervention will be manualised and quality controlled.
3. To obtain high rates of follow-up data on a minimum of 80% of those recruited into this trial at 12 months in order to provide a definitive answer to the research question and assess the longer-term outcomes of both interventions.
4. To analyse our results according to CONSORT and CHEERS guidelines
5. To disseminate the outcomes to the NHS, academic colleagues, relevant service user groups and the wider community.

<u>Existing research</u>

Recent NICE guidelines (1) established good evidence for low intensity psychological interventions in GAD. Step 1 interventions are usually delivered within primary care, involving identification, assessment, education and active GP monitoring. If symptoms persist referral to a step 2 low–intensity psychological intervention is recommended, e.g. self-help interventions or psycho-education groups, usually facilitated by a low-intensity IAPT psychological worker. However a significant number will not respond to these interventions and require ‘stepping up’ to more intensive Step 3 interventions.

Although there is evidence of the clinical and cost-effectiveness of sertraline for GAD compared with placebo, and also of CBT compared with wait-list controls (1), there have been no head to head comparisons of sertraline (or any other SSRI) versus CBT to evaluate which treatment is the most clinically and cost-effective. Currently NICE guidelines suggest that choice of treatment between a pharmacological or psychological treatment at step 3 should be based mainly on patient preference, although availability of CBT may determine whether patients have such a choice in some areas.

NICE conducted a systematic review of placebo-controlled antidepressants studies in generalised anxiety disorder (GAD) (1). Thirty four studies were identified which were generally of high quality though relatively short in duration (8-12 weeks). Of these trials, 17 involved SSRI while 16 involved SNRI (venlafaxine and duloxetine) treatment. Both of the SNRIs as well as paroxetine and escitalopram have marketing authorisations for the treatment of GAD. The NICE summary concluded that, relative to placebo, SNRI and SSRI treatments were efficacious in the treatment of GAD, in that they produced greater reductions in HAM-A ratings and increased the probability of response to treatment.

Generally, effect sizes of antidepressants relative to placebo were in the low to moderate range and did not apparently vary between the different antidepressants to a clinically meaningful extent. There was no clear evidence of a dose response relationship for any particular antidepressant. The most commonly experienced side effects with antidepressants were nausea and insomnia.

These placebo-controlled studies were generally not more than 12 weeks in duration but GAD is considered to be a chronic disorder. Therefore guidelines recommend continuation treatment in responders and a meta-analysis of available relapse prevention studies suggested an important effect of continuing effective pharmacological treatment for up to one year in patients with GAD who have responded to pharmacological therapy (12), although there is currently no evidence that sertraline is effective in preventing relapse (13).

In assessing the effectiveness of CBT or SSRIs, we need to consider clinical symptoms and functional impairment. It is also important to assess outcomes of more than a few months, given that most pharmacological studies do not have follow-ups of longer than 12 weeks (1) and there is some limited evidence that CBT may have a protective effect against future episodes (11). In assessing these factors associated costs and cost-effectiveness are crucial in making future recommendations.

Summary of proposed research

Background: Generalised Anxiety Disorder (GAD) is common, causes unpleasant symptoms and impairs people's functioning. It is often chronic and may be accompanied by depression and other anxiety disorders. Recent NICE guidelines have outlined the best initial treatments but it isn't clear whether medication or psychological therapy provides better long term outcomes for those not responding to simpler low intensity treatments.

Trial: We propose a randomised trial of the medication sertraline versus Cognitive Behavioural Therapy (CBT) for people with GAD who have not responded to low intensity psychological treatments.

Methods: We will recruit people via the Increasing Access to Psychological Therapies (IAPT) service from up to 15 sites in England. People still scoring highly on an anxiety measure (GAD-7) despite having received a low intensity psychological intervention will be given a study information sheet about the trial. The study information will explain that the medication being evaluated, sertraline, although not currently licensed for GAD was recommended by NICE on the basis of its effectiveness in clinical trials and that the study team will be available to clarify any issues arising from this. Those interested in taking part in the trial will be given an appointment to meet a research team member within one week and will be assessed against trial inclusion and exclusion criteria. They will need to be at least 18 years old and to meet psychiatric criteria (DSM-IV) for GAD assessed with a computerised version of a standardised psychiatric instrument called the MINI which will give DSM-IV diagnoses. We will also use this to assess if they have depressive symptoms and any other anxiety disorder. They will be excluded if they have current major depression or another anxiety disorder more troublesome to them than their GAD, significant dependence on alcohol or illicit drugs or have been prescribed any anti-depressant in the previous eight weeks or high intensity psychological therapy within the past 6 months.

Interventions: Eligible participants will be consented and randomised via an independent computerised system to one of two interventions. (a) The medication sertraline prescribed by their GP according to a trial protocol matching current clinical recommendations. We will inform the GP that their patient knows sertraline does not have a marketing authorisation for GAD and has agreed to being prescribed this. We will ask GPs to review patients regularly (at least 6 times in 12 months) and patients to take the medication for a year unless they have significant adverse effects. Side-effects will be regularly monitored. (b) The other intervention is CBT delivered by high intensity therapists from local IAPT services. They will provide 14 to 16 sessions of a manualised treatment developed for use in GAD and will be trained in its delivery. Sessions will be digitally recorded and a random 10% assessed for quality (fidelity to the manual and therapist competence) by an independent external rater according to pre-specified criteria.

Outcomes: Participants will be asked to self-complete the GAD-7, PHQ-9 and EQ-5D assessing their symptoms of GAD, depression and quality of life at baseline 3, 6, 9 and 12 months. They will also be asked to complete questionnaires assessing their levels of general functioning, other anxiety symptoms, quality of life and current use of health and social care at baseline and 12 months. We will compare the clinical and cost-effectiveness of the two treatments at 12 months.

Health technologies being assessed

(a) SSRI – Sertraline

The NICE Guidelines Advisory Group proposed sertraline as a first choice pharmacological treatment although this agent does not have a marketing authorisation for GAD and there are relatively few randomised trials (only two trials with 706 patients in total.) Nevertheless, in terms of risk of discontinuation due to adverse effects, sertraline was the best tolerated antidepressant and its availability as a generic made it the most cost-effective choice. Duloxetine (an SNRI) had a greater probability of producing clinical response in a network meta-analysis, but this is not commonly prescribed in UK primary care. The SSRIs paroxetine and escitalopram both have marketing authorisation for GAD and there is little pharmacological difference between them and the SSRI sertraline. However, paroxetine has a more marked withdrawal syndrome than sertraline and escitalopram is more expensive and can extend the QT interval.

In the two sertraline studies in GAD, sertraline was dosed flexibly between 50-150mg daily (mean dose at the end of treatment about 90mg). In one study sertraline was started at 25mg daily for one week to improve tolerance early in therapy and this is also recommended by the manufacturer in the licensed use of sertraline in post-traumatic stress disorder, social anxiety disorder, and panic disorder.

(b) Cognitive-Behavioural Treatment – (CBT)

There are a number of cognitive-behavioural models of GAD. Examples include the cognitive avoidance model (32), the metacognitive model (33) and the emotion dysregulation model (34). Dugas and colleagues have also developed a model of GAD, which is known as the intolerance of uncertainty model (35). Stated simply, the model proposes that negative beliefs about uncertainty (or intolerance of uncertainty) lead to difficulty dealing with real or imagined uncertainty-inducing situations, which can then lead to excessive worry and GAD. Research has shown a consistent and robust relationship between intolerance of uncertainty and GAD. For example, their relationship is not accounted for by shared variance with other anxiety disorders, mood disorders or negative affect (36), (37). Data also suggest that intolerance of uncertainty is a *causal risk factor* for high levels of worry and GAD. For example, changes in intolerance of uncertainty precede changes in worry over the course of treatment (38) and the experimental manipulation of intolerance of uncertainty leads to corresponding changes in worry and monitoring behaviour (39), (40). Thus, data from correlational, longitudinal, and experimental studies suggest that intolerance of uncertainty plays a key role in GAD.

The Dugas and collaborators model is one of three CBT protocols for GAD included in the UCL CBT Competences Framework (http://www.ucl.ac.uk/clinical-psychology/CORE/CBT_Framework.htm) which guides IAPT services how to carry out CBT effectively and in line with best practice. The treatment aims to help affected individuals develop beliefs about uncertainty that are less negative, rigid, and pervasive. This is accomplished with the use of treatment strategies (such as behavioural exposure to uncertainty, problem-solving training, and imaginal exposure) that aim to help patients confront uncertainty-inducing thoughts and situations. The treatment has been tested in four published randomized clinical trials, with results showing that it is more efficacious than wait-list control (23), (24), supportive therapy (25) and applied relaxation (26). The findings also show that 60 to 77% of patients attain GAD remission and that 50 to 55% achieve high end-state functioning following the treatment. The CBT protocol developed by Dugas and colleagues (i.e. based on the intolerance of uncertainty model of GAD) will be used in the proposed study (5).

Design and theoretical and conceptual framework

Time course: The comparison is between SSRI medication and CBT that are both active treatments. However, we think in a pragmatic trial that the time course of benefit is likely to differ. The SSRI medication may have a benefit earlier on but it is likely this effect could reduce over time, largely because many of the participants may stop taking their medication. In contrast, CBT is an educational approach that should be providing the participants with skills that they may use in the future. We would therefore expect that the CBT would continue to have benefit for the 12 month duration of the trial. As a result our hypothesis that CBT will lead to a better outcome than SSRIs applies to the 12 month follow-up.

Trial design

Participant randomised trial comparing treatment with Sertraline with high intensity CBT for service users with GAD who have failed to respond to low intensity psychological interventions recommended by NICE(1)

Setting

Community based & linked with local Improving Access to Psychological Therapy (IAPT) services. We will work with 5 recruitment sites in southern England the pilot phase and up to 15 sites across the whole of England in the full trial, with whom we have excellent links with local IAPT services in a range of urban, suburban & more rural settings. Our agreed IAPT pilot sites are in the London boroughs of Camden & Islington, East London and Bexley as well as sites in Sussex and Warwick and have sent in formal letters of agreement to participate (appendix).

Recruitment of participants

People who have not responded to step 2 low intensity psychological interventions for anxiety or depression who are being considered for a step 3 intervention within their local IAPT services will be eligible. Identification will be by low intensity (LI) IAPT workers reviewing the patients who routinely administer the GAD-7 anxiety measure (3) and PHQ-9 depression measure (4). Those scoring 10 or more on GAD-7 will be given an outline study information sheet at that appointment and if they are interested in taking part their permission will be sought for contact by the research team.

The research team (trial manager / research assistant) will be faxed the details of potential participants and respond within one week (preferably by 'phone or email or if not by letter) offering them an appointment at the IAPT premises or their own home – whichever is preferred. A full study information sheet will be included at this stage. At the recruitment appointment the researcher will check that the patient understands the reasons for the study and any queries will be addressed. It will be confirmed at this point that they are interested in taking part, on the understanding that if randomised to the drug arm they will be receiving the SSRI sertraline which, although proposed for use outwith a marketing authorisation for GAD, was recommended by NICE on the basis of its effectiveness in clinical trials. Those agreeing to take part will be checked for eligibility before being asked to give fully informed consent.

Baseline assessment

The baseline interview and assessment will be conducted by a member of the research team (trial manager or research assistant).They will confirm that the patient has read and understood the study information leaflet and answer any queries. If they are happy to proceed they will check the inclusion and exclusion criteria, administering the relevant sections of the Mini International Psychiatric Interview (MINI) questionnaire (depression, panic, social anxiety, alcohol and substance misuse and GAD). If the potential participant fulfils the DSM-IV criteria for GAD they will be asked to confirm whether their GAD or worry symptoms are of more severity and concern to them than any symptoms they may have associated with psychological co-morbidities such as depression and other anxiety disorders, and that this is an important problem for them that they wish to address.

If the person fulfils the eligibility criteria and wishes to participate informed consent will be taken. The researcher will administer the HAM-A questionnaire and then ask the participant to complete the primary and secondary outcome measures at baseline whilst s/he randomises the participant via the web system. In this way we should have 100% completion of measures at baseline and the participant will be informed about their intervention group before leaving the interview. They will also be given all the relevant information about the further steps involved in either the SSRI or CBT arm depending on which applies to them.

Inclusion Criteria:
Aged 18 or above
Positive score of 10+ on GAD-7
Primary diagnosis of GAD as diagnosed on MINI
Failure to respond to NICE defined low intensity interventions

Exclusion Criteria:
Inability to complete questionnaires due to insufficient English or cognitive impairment
Current major depression
Other comorbid anxiety disorder(s) of more severity or distress to the participant than their GAD
Significant dependence on alcohol or illicit drugs
Comorbid psychotic disorder, bipolar disorder
Treatment with antidepressants in past 8 weeks or any high intensity psychological therapy within past 6 months

Randomisation and allocation of participants to trial groups
Eligible consenting participants randomised to one of two intervention arms via an independent computerised service provided by the PRIMENT CTU. The randomisation will be stratified by depressive symptoms.

Methods to protect against other sources of bias

The trial will be conducted according to GCP and to the highest methodological standards ensuring that randomisation is concealed, that treatments are delivered appropriately to each experimental condition and cross over is minimised, that loss to follow up will be minimised and certainly less than 20% (we have achieved substantially higher follow up rates), that the data collection, management and analyses are all conducted according to established guidelines and SOPs within the PRIMENT Trials unit and the analyses according to a pre-specified statistical analysis plan. We will publish the trial methods in advance of data base lock. Results will be published in full in a timely manner and according to CONSORT guidelines.

Planned interventions

Trial arm 1 – SSRI – Sertraline

The SSRI to be prescribed for the participants randomised to this arm is sertraline. Potential participants will have been informed by the low intensity IAPT worker and in the information sheet that sertraline does not have a marketing authorisation for GAD but was recommended by NICE on the basis of its effectiveness in GAD clinical trials and will have agreed to be prescribed this if so randomised. The patient's GP will be informed and asked to prescribe sertraline following a detailed protocol and to review participants at least 6 times over the 12 month follow-up during which they will be advised to continue the medication provided they experience no significant adverse effects. We have conducted a modest survey of 12 GPs in a range of local boroughs in London (Camden & Islington, Barnet, Haringey and Brixton) and all those canvassed said they would be happy to do this if approached by a research team with appropriate information and guidance as to how to proceed with the protocol for prescribing and reviewing their patient's care. The most important elements of the protocol are as follows:
(i) Participants randomised to the SSRI treatment arm will be asked to provide the researcher with their GP contact details. They will then be asked to deliver a letter to the GP from the research team outlining the details of the trial and what will be requested of the GP, and to make an appointment to see them to discuss the treatment. We will also fax a copy of this letter and the patient's consent to participate in the trial to the GP.
(ii) Our intention is for the GP to prescribe sertraline in accordance with usual clinical practice. At the initial appointment the GP will be asked to consider the following: to confirm that they have not been taking any other prescribed antidepressant in the past 8 weeks; previous treatment response if applicable; risks of self-harm or deliberate overdose; tolerability and side-effects; possible interactions with concomitant medication; that the patient agrees to proceed with the suggested treatment
(iii) The GP will then need to reaffirm that the patient understands that although sertraline does not have specific marketing authorisation for GAD, it was recommended by NICE on the basis of its effectiveness in GAD clinical trials and the patient is asked to give their informed consent to having it prescribed – prescribing the drug on this basis should be documented in the patient's GP notes
(iv) The recommended starting dose in this trial will be 25mg Sertraline daily for one to two weeks to improve tolerance early in therapy. The GP will explain that the patient will need to cut 50mg tablets prescribed in half, as there is currently no 25mg tablet form available. A brief explanation of the most likely possible side-effects

should be given and the appropriate action to be taken in such circumstances. If the patient tolerates the 25mg dose for a week they should be advised to increase to a whole tablet or 50mg daily.
(v) The GP should review the patient within the first two weeks of starting the medication and check for acceptability, concordance and any side-effects from the medication. If the patient agrees to continue taking the medication they should increase the dose of sertraline to 50mg daily if they have not already done so. We will not stipulate how the GP should review the patient's progress but suggest that they use their normal (treatment as usual) procedures to do this. If this involves asking the patient to complete an appropriate self-complete questionnaire assessing anxiety they will be asked to avoid using the GAD-7 for this purpose, given that this is the primary outcome measure for the trial and to use an alternative – e.g. the Hamilton Anxiety and Depression Scale (HADS). Any such use should be documented. They may rely purely on their clinical judgement and the patient's feedback if this is their usual practice.
(vi) Further reviews should be arranged at 6 and 12 weeks, at which the efficacy of the medication and any potential side-effects should be assessed. The anticipation is that the usual treatment dose will be between 50 and 100 mg for most patients, although some might require 150mg
(vii) We would expect the patient and prescriber to report some or significant improvement by six weeks, with this being well established by 12 weeks. We will be asking the GPs to ask about and note functional change (occupational and social) as well as clinical improvement. Minimal improvement after 12 weeks at a maximal tolerated dose should prompt consideration of change of treatment
(viii) If the patient cannot tolerate sertraline or has not responded, we will recommend that the GP prescribes an alternative SSRI or SNRI antidepressant in accord with NICE guidelines. Any changes in medication will be recorded by the GP and the data collected by the study team.
(ix) The GP will be acting in the best interests of the participant at all times, so if indicated will be able to refer to secondary care services or psychological treatments. These will be recorded by the GP and the information collected by the trial team. We do not anticipate that trial participants in the SSRI will be referred and in receipt of CBT very often during the trial period as there are often long waiting-lists.
(x) If the patient makes any interim visits to the surgery to discuss their treatment for GAD or issues to do with the medication being received these should be clearly documented in their notes.(We have costed for up to four additional visits per GP)
(xi) If the patient agrees to continue with the sertraline as prescribed and both the GP and patient consider that there has been an adequate therapeutic benefit then there should be a further review at 26 weeks (6 months) and again at 52 weeks (12 months).
(xii) The GP will be expected to record any adverse events and to inform the study team promptly of any serious adverse events
(xiii) There will also be external quality control and monitoring procedures conducted as detailed below and in the research governance and project management sections later in this protocol.

GP manual and monitoring visits
The research team will produce a detailed manual outlining the practice and procedures they would like the participating GPs to follow during the intervention visits. This will be based on the protocol described above. We will not be providing any formal training for the GPs in providing such care we wish this to mimic routine practice. The treatment steps, however, will be detailed in the drug intervention manual. Monitoring visits will be conducted by the PRIMENT CTU team who will explain the drug monitoring procedures which they will be asked to follow and ensure that they are comfortable with both the contents of the trial manual and the web based procedures required to input data for the drug monitoring.

***Trial arm 2* - Cognitive-Behavioural Treatment**

Procedures
CBT will consist of 14 (+ or - 2) weekly 50-minute sessions and will cover 6 treatment modules: psycho-education and worry awareness training; re-evaluation of the usefulness of worry; uncertainty recognition and behavioural exposure; problem-solving training; written exposure; and relapse prevention. **(1) Psycho-education and worry awareness training:** The first few sessions of treatment are devoted to psychoeducation Patients begin to monitor their worrying on a day-to-day basis, and learn to distinguish between worries about current problems and worries about hypothetical situations **(2) Re-evaluation of the usefulness of worry:** Patients identify and re-evaluate their positive beliefs about worry using strategies such as role-play and hypothesis testing. Patients are helped recognize that their beliefs about the usefulness of worry are interpretations and not facts and begin the process of "imagining a life without worry." **(3) Uncertainty recognition and behavioural exposure:** Participants learn that intolerance of uncertainty contributes to worry and anxiety and that uncertainty-inducing situations are largely unavoidable. They then learn to seek out and experience uncertainty-inducing situations. One noteworthy advantage to seeking out uncertainty is that patients

begin to add some variety and flexibility to their daily lives (which runs counter to the rigidity they are often accustomed to). In fact, many patients report that these exercises are unexpectedly positive experiences that provide a sense of mastery and freedom. **(4) Problem-solving training:** For *worries about current problems*, participants learn to use a problem-solving procedure targeting problem orientation, problem definition and goal formulation, generation of alternative solutions, decision making, and solution implementation and verification (41). In the current CBT protocol, problem-solving training emphasises the role of uncertainty in both the problematic situation and the problem-solving process, and the distinction between the passive process of worry and the active process of problem solving. **(5) Written exposure:** In the field of health psychology, a method known as written emotional disclosure has been shown to lead to positive health outcomes (42). Patients are asked to write about the same feared scenario three times a week, with each writing session lasting 30 minutes. Written exposure sessions are continued until writing about the feared outcome no longer provokes anxiety (typically 8 to 10 exposure sessions). **(6) Relapse prevention:** The final component is relapse prevention, the aim of which is to consolidate the attitudes, beliefs, and skills acquired during therapy. Patients are also encouraged to continue practicing their new skills and prepare for stressors that may arise.

Training in the Protocol
An initial two-day training in the protocol will be provided by Professor Michel Dugas (MD). Therapists, supervisors and research team members will attend the training which will be video-taped. Participants will have read the treatment manual before the training which comprises didactic methods, DVD demonstrations and role-plays. Therapists and supervisors will be asked to complete a knowledge and skills assessment before and after the training. Therapists and supervisors will also attend 2-day training sessions provided by MD and Professor Roz Shafran (RS) during the study. We anticipate that these workshops will need to be run once for the pilot and once or twice for IAPT high intensity therapists involved in the main trial. RS may provide individual training for replacement therapists who come on board later in the trial. As part of the training, therapists will be asked to treat 1 or 2 patients in a pilot phase. The adherence and competence will be assessed (see below) and only when therapists meet the threshold for competence and adherence will they see patients as part of the trial. Each service will be asked to nominate a specialist supervisor for the duration of the project. All IAPT supervisors will have attended the general supervision training.

Comorbidity
We will expect there will be circumstances when the therapists also identify comorbidities in addition to GAD. In these circumstances, the therapist will also need to address comorbidities using the appropriate CBT techniques. This would correspond to good clinical practice in the NHS. We will provide the therapists and supervisors with guidance about the CBT approaches to use when they encounter the common comorbidities

CBT - Integrity
Following published guidelines (43), we will assess treatment integrity by monitoring adherence/fidelity to the CBT protocol and therapist competence. To assess **treatment adherence/fidelity**, all CBT sessions will be digitally recorded and 10% (randomly chosen) will be rated for adherence to the treatment manual by an external rater using the *Treatment Intervention Checklist*, which lists permitted and prohibited interventions. To assess **therapist competence**, an independent expert therapist will apply the *Revised Cognitive Therapy Scales* (44) to 10% (randomly chosen) sessions. The assessment of both adherence/fidelity and competence is extremely important in this type of study because the validity of psychotherapy cannot be established without high ratings on both measures. For example, high adherence and low competence might indicate that the treatment was delivered in a rigid, mechanistic, and non-empathetic fashion

Proposed duration of the intervention
The high intensity CBT intervention will be delivered over 14 to 16 weekly sessions and we expect this to be completed within 6 months of randomisation. We will ask the GPs prescribing Sertraline and the participants taking this medication to continue doing so for 12 months as recommended by NICE guidelines to investigate longer-term effectiveness.

Usual care by GP
In addition to the CBT provided by the IAPT services, the participants randomised to this arm will also receive usual care as provided by their general practitioner. The GP will be informed that the participant is receiving CBT and the nature of the study. However, there may be occasions when the GP thinks that additional SSRI or SNRI medication is indicated. This information will be collected by the study team.

Proposed outcome measures and other measurement

Primary Outcome

- **GAD-7** - a 7 item self-complete questionnaire with very good sensitivity (89%) and specificity (82%) for GAD. It is one of the core measures regularly administered by the IAPT services (3).

Secondary Outcomes

- **Hamilton Anxiety Rating Scale (HAM-A)** – This is a 14 item observer rated anxiety scale which has been widely used, particularly in pharmacological studies (7).
- **Patient Health Questionnaire (PHQ-9) -** This is a 9 item self-rate scale widely used to monitor the severity of depression. It is also one of the core IAPT measures (4).
- **Work and Social Activity Scale (WASAS) -** This is a 5 item self-complete questionnaire which we will use to asses participants' difficulties with physical and social functioning (8).
- **Euroquol (EQ 5D) –** a 5 item self-complete measure used to assess quality of life and calculate utility scores for QALYs (9)
- **Client Service Receipt Inventory (CSRI) -** Data on services used and productivity losses will be collected using a modified version of the Client Service Receipt Inventory (10).
- **Patient acceptability measure –** our PPI representatives are developing this measure.
- **Patient preference rating scale –** we will use a 4 item Likert scale used by our team in other studies

Serious Adverse Events Monitoring Form. We will use the standard SAE template provided by PRIMENT CTU. An adapted version of this template has been used in a trial of psychological interventions (CANTALK)

Health Service Outcomes

We will collect health service use data from both intervention arms at the 12 month treatment completion point as follows: GP consultations coded for GAD and psychotropic drug prescriptions over the 12 month study period from the GP surgeries and patient attendance rates at the IAPT sites

Proposed frequency and duration of follow-up

Measure	Time 0	3 months	6 months	9 months	12 months
GAD-7	√	√	√	√	√
HAM-A	√				√
PHQ-9	√	√	√	√	√
WSAS	√				√
EQ 5D	√	√	√	√	√
CSRI	√				√
Patient preference rating scale	√				√
Treatment acceptability scale	√				√
Health service outcomes					√

The primary outcome (GAD-7) will be collected 3 monthly for the 12 months duration of the study, as will the PHQ-9 and EQ-5D.
Other secondary outcomes will be assessed at baseline and repeated at 12 months (see table).

It is usual practice for patients in receipt of IAPT treatment services to be asked to complete both a PHQ-9 (a brief self-report measure of depression) and GAD-7 at each attendance for service monitoring rather than clinical purposes, As we will be collecting this data as part of the outcome measures for this trial and do not want to impact on the accuracy of this data collection it has been agreed with the participating IAPT sites that they will not routinely collect this data for patients in receipt of their service who are also in the trial.

Final Assessment at 12 months:

The research team will carry out the HAM-A on all participants at 12 months and encourage them to complete all the 12 month outcome measures at this point to ensure optimum data collection. This will be a different member of the research team from the original assessor.

Proposed sample size

The principal outcome variable is the change from baseline to 12 months in the GAD-7, which we will compare between treatment groups in a regression model that includes baseline score as a covariate. Tests and confidence intervals for treatment effects will be based on the normal distribution - an assumption justified by the central limit theorem. Estimates for the standard deviation (SD) of GAD-7 scores are available from Spitzer et al (3). There, SDs of just under 5 were found for two groups of patients - those diagnosed with GAD (SD=4.7) and those without (SD=4.8). Therefore, we have used an estimate of 5 for the SD of our outcome measure, overlaid with an additional component of variance (essentially due to therapist) sufficient to give an intra-cluster correlation coefficient of 0.02. Then, making the conservative assumption of a cluster size of 7, and an allowance of 20% for dropout and other challenges, means we require a total sample-size of 360 patients to detect a ('true') average difference of 2 between treatments with 90% power at $p<0.05$ (2-sided). Further, the expected half-width of the 95% confidence interval for the treatment difference is then 1.2. With this sample size, we retain over 80% power should the ICC turn out to be 0.05 rather than 0.02. Alternatively, with this sample size, we retain 80% power should the SD of our outcome measure turn out to be 5.8 rather than 5. The design has the advantage of providing robust interpretation in a number of circumstances due to the planned precision. Thus with no impact upon alpha spending, it will be possible to interpret a significant difference between the groups of greater than 2 points as also being clinically relevant, and additionally a non-significant result that excludes a difference of 2 points (i.e. the upper confidence interval range <2) as demonstrating non-inferiority. Further, a non-significant difference where the outer bands of the confidence interval are less than ±2 points on the GAD-7 will indicate equivalence. Indeed, the planned precision of the trial is such that it should provide a firm basis for decision-making even if opinions as to the correct size of the minimally important difference alter somewhat before the results become available.

Statistical analysis of clinical data

The principal analyses will be conducted according to a pre-specified statistical analysis plan which will be finalised before database lock. The principal analyses will be conducted according to the intention to treat principle using generalised mixed models. The primary analysis will use a generalised mixed model accounting for clustering of therapist effects, investigational sites (both as random effects) and a limited number of pre-specified patient level factors including the baseline GAD-7 score and the presence of co-morbid depression. The principal analyses will be based upon available data and supportive analyses will examine the extent to which the principal analyses are robust to the challenge presented by the observed loss to follow up. Exploratory analyses will be carried out to describe how patient preferences along with a limited number of other pre-specified characteristics of participants may modify treatment effects (45). We will adhere to the CONSORT guidelines in the analysis and reporting of the trial.

Economic evaluation

We will calculate the net monetary benefit (NMB) of CBT compared to SSRIs for patients with persistent GAD which has not improved with low intensity psychological interventions. Health and social care resource use will be collected for both interventions over the 12 month duration of the trial using patient GP files where possible and a significantly reduced version of the CSRI, focusing mostly on secondary acute care and mental health care contacts. Resource use will be multiplied by costs from nationally published sources to calculate the total cost per patient. The health care resource use associated with the intervention will also be captured in both arms: the cost of SSRIs and any follow up, training or monitoring costs; the cost of CBT based on the number of sessions attended per patient, session duration, the staff type and grade delivering the CBT, training and any overhead costs. The mean cost per patient for SSRIs and CBT will be calculated and confidence intervals reported, calculated using non-parametric bootstrapping with replacement. The mean QALY per patient will be calculated from the EQ-5D and the UK algorithm for calculating utility scores. The EQ-5D will be collected at baseline, 6 and 12 months to allow us to calculate the area under the curve over the 12 month trial duration for the SSRI group and CBT group, adjusting for baseline differences. The net monetary benefit (NMB) of both interventions will be calculated for a range of values of willingness to pay (WTP) for a QALY. Confidence intervals will be constructed using non-parametric bootstrapping. A cost-effectiveness acceptability curve (CEAC) will report the percentage of times that each intervention has the highest NMB for a range of values of WTP for a QALY. One, two and multi way sensitivity analysis will be conducted for any assumptions made.

Recruitment rate

To date there have been few larger scale trials recruiting from IAPT services and none to our knowledge that have recruited from the caseloads of low intensity IAPT staff. Three of the investigators (JC, MS and RS) have experience of working with IAPT services as researchers, trainers and service leads and will liaise between the research team and IAPT study sites to ensure local understanding of recruitment procedures and assist in troubleshooting problems. Identification and training of a local CBT supervisor for IAPT therapists in the CBT arm will put in place a lead local clinician with an investment in facilitating recruitment. Fifteen IAPT sites will be used for the study in order to reduce the demands on each site.

We have examined the IAPT data for 2 local London boroughs with a combined population of 400,000 during the year 2011-2012 when 6,569 people were referred to their IAPT services. Within this population 615 people (11%) had a GAD-7 score of 10 or above and were also given a provisional diagnosis of GAD by the low intensity therapist seeing them. Of these, 89 people (14%) during the year were stepped up from a low intensity to high intensity intervention and would have been potential candidates for our trial. Step-up rates from another site in Reading ranged from 15 to 20%.

In order to recruit sufficient people for this trial we need to recruit a total of 360 people which equates to 24 participants per study site if there are15 sites. We plan to pilot our recruitment methods in 5 IAPT sites in London, South and Central England who have agreed to take part in this stage. They will provide a range of populations; the London boroughs of Camden & Islington and East London (urban), Bexley and Warwick (suburban) and West Sussex (suburban and/semi-rural). During our pilot recruitment phase we will initially work on forming relationships with the local low intensity IAPT workers, ensuring they are clear as to what is required and testing our recruitment methods (end of January to end of April 2015). We will then aim to recruit 2 participants per month from each of these 5 pilot sites for the 9 months from the end of April 2015 to the end of January 2016, resulting in a total planned recruitment of 90 participants during this pilot phase (i.e. 25% of our planned total recruitment of 360 participants).

We will also be consolidating our relationships with a further 10 sites throughout England during this time, so that we are in a good position to recruit the remaining 170 participants over the next 12 months of the main trial recruitment period (February 2016 to the end of January 2017). This should be achieved at a recruitment rate of 2 participants per site per month for 12 months for the new main trial sites, which we consider feasible given the figures above. The pilot sites will continue recruiting and treating patients until they reach their target of 24 participants. We will review the situation as regards recruitment across the whole study before asking any sites to stop recruiting, as it may be that some sites will recruit better than others, but the aim is to have similar numbers across all the sites.

Internal Pilot

The pilot phase will run in 5 IAPT sites within inner and outer London, south and central England. We aim to recruit 25% of the total sample in this phase of the study at a rate of 2 participants per month per site, which we consider feasible given data from our local site in Camden & Islington presented above. The methodology of the pilot phase will be essentially the same as the full trial to enable combination of the data from both phases for analysis, but we will refine our recruitment strategies from the pilot phase will be applied to the main trial. We will also collect the primary outcome measure the GAD-7 at baseline, 3 and 6 months from all the participants recruited in the pilot phase to monitor our response rates and see whether we need to adjust strategies for their collection. We have extended our pilot phase from 9 months to 12 months (end of January 2015 to end of January 2016) to enable these aspects to be covered.

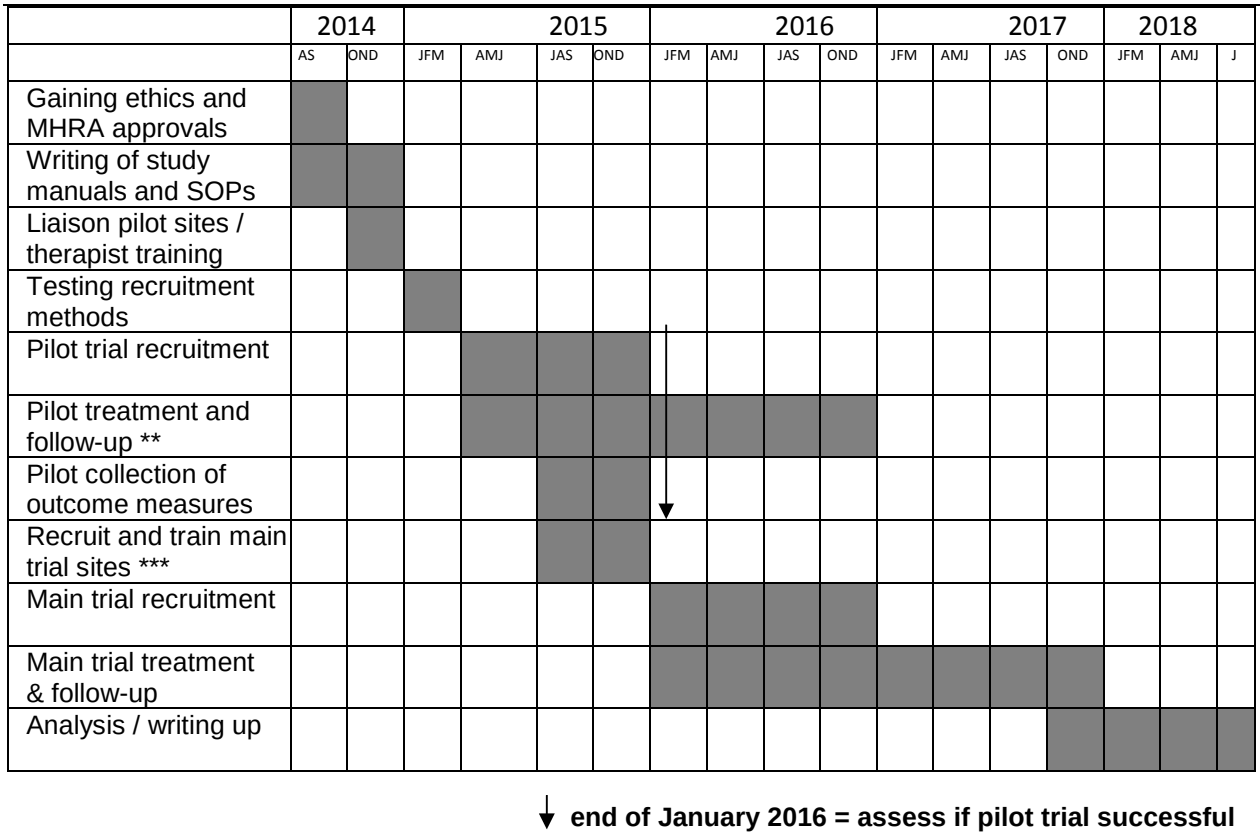
The criteria for judging the success of the pilot phase and proceeding to full trial will be based on:

(i) Recruitment: We will aim to recruit a minimum of 70% of the pilot trial recruitment target of 90 consented participants (25% of the full trial total). This translates into the recruitment of a minimum of 63 consented participants across 5 IAPT sites by the end of the pilot 12 months with a mean of 12 recruits per IAPT site
(ii) Outcome data: We will aim to collect complete data for the GAD-7 for at least 70% of participants at 3 and 6 months follow-up in the pilot trial

(iii) Fidelity of the CBT treatment: All CBT consultations which are part of the trial will be digitally recorded and we will conduct external fidelity checks on a random 10% of these to assess fidelity to the GAD CBT protocol being used. We will aim for 80% fidelity to the treatment as described in the manual.
(iv) Adherence to treatment: We will aim for at least 60% of participants to have started sertraline at a therapeutic dose of 50mg or above by 4 weeks or to have engaged with the CBT treatment by attending the first session.

All the criteria below will be closely monitored during the internal pilot and data collected at 3 monthly intervals during the 9 month recruitment phase of the internal pilot, with the assessment against the progression criteria currently timed to take place at the end of January 2016 although this may be later if there any delays to the start of the study.

Project timetable and milestones



** We will have to offer treatment to completion to any participants recruited to the pilot trial even if the decision is made not to proceed to the full trial.
*** We will also have to start training therapists at the other sites in preparation for the full trial before the final decision as to whether or not to proceed with the full trial is made

Service users

Dr Thomas Kabir (Mental Health Research Network - MHRN - Service Users Research Coordinator) is a co-applicant and Megan Rees (MHRN – Patient and Public Engagement Coordinator) is a collaborator. Both have commented on and contributed to the proposal, particularly as regards discussion of the outcome measures to be used (including PROMs), recording patient treatment preferences at baseline, clarifying eligibility criteria and the potential constituents of both treatment arms and have advised about dissemination of future results.

They will help us recruit two or three service users with anxiety disorders from the MHRN service user group to form a Clinical Advisory Group (CAG) which will report directly to the Trial Management Group (TMG) and

to Megan and Thomas who will be members of our Trial Steering Group (TSG). The CAG will be asked to help develop the participant information resources – this is particularly important given that the information to be given to potential participants is quite complex, as the pharmacological agent sertraline, although known to be effective in GAD, does not currently have specific marketing authorisation for this use. This will need to be carefully explained in the study information sheet, as well as the rationale for the trial itself. They are also going to work with the CAG to help us develop a tailored patient acceptability questionnaire for this trial. The CAG will also comment on the results of the research and how these should be wider community for implementation. They will meet twice a year throughout the trial and will be actively supported by the Trial Manager and Chief Investigator

Research Governance

Sponsorship
The trial will be sponsored by University College London.

Trial Management
The trial will be run through the NIHR UKCRC registered PRIMENT Clinical Trials Unit, which provides specialist expertise in the design, conduct and analyses of trials in primary care and mental health. The trial will be set up and conducted in accordance with JRO (UCL) Quality Management Systems and SOPs for CTIMPs.

Trial Management Team
Day to day responsibility will be managed by the Chief Investigator in close collaboration with the Trial Manager and assistant members of the trial team, with responsibilities clearly delegated. The trial management team will ensure that the trial is conducted, recorded and reported in accordance with the protocol, good clinical practice, all regulatory requirements and other essential procedures for running trials as documented by the SOPs developed by the PRIMENT CTU and the Sponsor.

Trial Management Group
A Trial Management Group (TMG) consisting of the PI, co-applicants, trial manager, trial statistician and any other individuals providing trial-specific additional expertise will meet every two weeks in the first three months during the set up phase and then monthly thereafter to monitor the conduct and progress of the trial. The division of responsibilities for the TMG will be defined following CTU/Sponsor SOPs and conducted accordingly.

Trial Steering Committee
The following independent external experts and lay representative have kindly agreed to be involved in the Trial Steering Committee (TSC).

Professor Chris Williams, Professor of Psychosocial Psychiatry at Glasgow University will Chair the TSC.
Professor Carolyn Chew-Graham, Professor of General Practice Research at Keele University will be the independent primary care representative
Dr Nicola Wiles Reader in Epidemiology, School of Social and Community Medicine at the University of Bristol will provide independent epidemiological expertise.
Mr Paul Lanham, until recently trustee / director of Depression Alliance will provide independent PPI input.

The TSC will meet once or twice per year during the project (up to 6 times in total). The Terms of Reference for the TSC will be to supervise the progress of the trial towards its objectives, to review at regular intervals relevant information from other sources (e.g. other related trials), and receive regular reports from the DMEC, in accordance with Sponsor/PRIMENT CTU SOPs.

Independent Data Monitoring Committee
We also have agreement from the following external experts who have kindly agreed to form an Independent Data Monitoring Committee (IDMC)

Dr Victoria Cornelius, Senior Lecturer in Medical Statistics, Department of Primary Care and Public Health Sciences, Kings College London will chair this committee.
Dr Michael Moore, Reader in Primary Care Research, University of Southampton and Divisional Lead CRN Wessex will provide independent primary care input.

Dr Charlotte Connor, Senior Research Fellow in Psychology, CLAHRC, Birmingham & Solihull Mental Health Trust and Honorary Senior Research Fellow, University of Birmingham will provide independent expertise in the field of psychological therapies.

The IDMC will meet three or four times during the study in order to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial in accordance with Sponsor/PRIMENT CTU SOPs.

Ethics and Regulatory requirements

Ethical review/regulatory compliance
The sponsor will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body (MHRA in UK) and a main research ethics committee, prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

Before any site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee must apply for NHS permission from their Trust Research & Development (R&D) and be granted written permission. It is the responsibility of the CI/PI or designee at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial. The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the MHRA and main REC within 1 year after the end of the trial.

Informed Consent
It is the responsibility of the CI/PI, or a person delegated by the CI/PI to obtain written informed consent from each subject prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. Adequate time must be given for consideration by the patient before taking part. The Investigator must record when the patient information sheet (PIS) has been given to the patient.

The Investigator or designee will explain the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason. No clinical trial procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into trial.

A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes. If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate.

Monitoring and Audit

The trial will be monitored according to the monitoring plan agreed by the Sponsor, based on the trial risk assessment. The risk assessment and subsequent monitoring plan will be regularly reviewed in case of any changes during the course of the study. Monitoring of the trial will consist of central monitoring and on-site visits to be determined by the plan, by appropriately qualified and trained members of the trial management team overseen by the Chief Investigator in conjunction with the Sponsor.
The trial may be subject to inspection and audit by the Sponsor/CTU and other regulatory bodies to ensure compliance with GCP.

Data Management

All data will be handled in accordance with the UK Data Protection Act 1998.
The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. The subject's initials, date of birth and trial identification number, will be used for identification.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

Training

All trial staff will undertake GCP training prior to undertaking any responsibilities on the trial. This training will be updated every two years in accordance with Sponsor requirements. Participating site training will be provided by the trial management team in accordance with Sponsor/CTU standard operating procedures.

Expertise

We have significant expertise in large national RCTS, with co-applicants providing epidemiological, CTU triallist, statistical and health economics input. We have expert PPI and psycho-pharmacology advice, specialists in training, supervision and rating of CBT programmes relevant to this bid, and co-applicants with strong links with IAPT our psychological therapy provider

UCL JRO

UCL regulatory oversight of conduct in the set up phase and during the trial are clear responsibilities of the Sponsor as set out in the Regulations and therefore a necessary cost for this trial. Oversight includes review of all documentation and submissions to ensure compliance with the Regulations, the contract services required, and specific technical advice and input with regards to IMP and pharmacovigilance.

Dissemination and projected outputs:

We will disseminate our findings in a variety of ways:

(i) Conferences: At national and international academic conferences; in particular the Society of Academic Primary Care, the Royal College of Psychiatrists, the British Psychological Society, the British Association of Behavioural & Cognitive Psychotherapy and the New Savoy Partnership, Canadian Psychological Association, Canadian Association for Cognitive and Behavioural Therapies, Canadian Psychiatric Association and annual meeting of the American Psychiatric Association. We will also present the results at local conferences or meetings arranged by R&D departments or clinical commissioning groups in regions where the research has taken place.

(ii) Journals: The trial will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement for the results (http://www.consort-statement.org/). We aim to publish in high ranking national and international peer-reviewed journals to reach the primary care, psychology and mental health community such as the Lancet or JAMA Psychiatry. We will also contact the free publications received by most UK GPs and the British Association of Behavioural and Cognitive Psychotherapy journal circulated to psychologists to ask them to publicise the results.

(iii) Clinicians: Through our links with the Royal College of General Practitioners and leaders of the IAPT community and our close links with the British Association of Behavioural and Cognitive Psychotherapy and the British Association of Counselling and Psychotherapy we will ensure that both the primary care community and the IAPT community are informed of our results.

(iv) NHS: We will ensure that the results are communicated to NHS England (previously the NHS Commissioning Board) and that they are disseminated to local Clinical Commissioning Groups.

(v) NICE: We will ensure that the National Institute for Health and Clinical Excellence (NICE) are made aware of the results of this trial which follows directly from their recommendation in the GAD updated guidelines and anticipate that the results of this trial will be published in the next version of the guidelines.

(vi) Service users: We will take advice from our service user representatives as to the best way to circulate results to their community. This is likely to include the organisations Mind, No Panic and Anxiety UK, with which we already have links. We will also access organisations in North America through our co-applicant (Dugas); these will include the Anxiety Disorders Association of Canada and Anxiety Disorders Association of America.

(vii) Public: We are working on a public campaign to raise awareness of anxiety disorders in general and GAD in particular to encourage those with symptoms to come forward for effective treatment. This is part of an ongoing project in the host department at UCL and we will include the results of this trial. UCL has a press office which connects with a variety of bodies, including journalists to expert academics and promotes UCL research and teaching throughout the global media.

(viii) Web-sites: We will publicise our results on the UCL web-site and also liaise with relevant service user organisations to make web-site links, e.g. via NHS Choices (http://www.nhs.uk/News/Pages/NewsIndex.aspx) and Patients like Me (http://www.patientslikeme.com).

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