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Marta Buszewicz,[1]* John Cape,[2] Marc Serfaty,[3,4] Roz Shafran,[5] Thomas Kabir,[6] Peter Tyrer,[7] Caroline S Clarke[1] and Irwin Nazareth[1]

[1]Research Department of Primary Care and Population Health, University College London, London, UK
[2]Department of Clinical Health Psychology, University College London, London, UK
[3]Division of Psychiatry, University College London, London, UK
[4]The Priory Hospital North London, The Bourne, London, UK
[5]UCL Great Ormond Street Institute of Child Health, University College London, London, UK
[6]McPin Foundation, London, UK
[7]Centre for Mental Health, Imperial College London, London, UK

*Corresponding author

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Abstract

Pilot of a 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 treatments as defined by the National Institute for Health and Care Excellence guidelines

Marta Buszewicz,[1]* John Cape,[2] Marc Serfaty,[3,4] Roz Shafran,[5] Thomas Kabir,[6] Peter Tyrer,[7] Caroline S Clarke[1] and Irwin Nazareth[1]

[1]Research Department of Primary Care and Population Health, University College London, London, UK
[2]Department of Clinical Health Psychology, University College London, London, UK
[3]Division of Psychiatry, University College London, London, UK
[4]The Priory Hospital North London, The Bourne, London, UK
[5]UCL Great Ormond Street Institute of Child Health, University College London, London, UK
[6]McPin Foundation, London, UK
[7]Centre for Mental Health, Imperial College London, London, UK

*Corresponding author m.buszewicz@ucl.ac.uk

Background: Generalised anxiety disorder (GAD) is common, causing unpleasant symptoms and impaired functioning. The National Institute for Health and Care Excellence (NICE) guidelines have established good evidence for low-intensity psychological interventions, but a significant number of patients will not respond and require more intensive step 3 interventions, recommended as either high-intensity cognitive behavioural therapy (CBT) or a pharmacological treatment such as sertraline. However, there are no head-to-head comparisons evaluating which is more clinically effective and cost-effective, and current guidelines suggest that treatment choice at step 3 is based mainly on patient preference.

Objectives: To assess clinical effectiveness and cost-effectiveness at 12 months of treatment with the selective serotonin reuptake inhibitor (SSRI) sertraline compared with CBT for patients with persistent GAD not improved with NICE-defined low-intensity psychological interventions.

Design: Participant randomised trial comparing treatment with sertraline with high-intensity CBT for patients with GAD who had not responded to low-intensity psychological interventions.

Setting: Community-based recruitment from local Improving Access to Psychological Therapies (IAPT) services. Four pilot services located in urban, suburban and semirural settings.

Participants: People considered likely to have GAD and not responding to low-intensity psychological interventions identified at review by IAPT psychological well-being practitioners (PWPs). Those scoring ≥ 10 on the Generalised Anxiety Disorder-7 (GAD-7) anxiety measure were asked to consider involvement in the trial.

Inclusion criteria: Aged ≥ 18 years, a score of ≥ 10 on the GAD-7, a primary diagnosis of GAD diagnosed on the Mini International Neuropsychiatric Interview questionnaire and failure to respond to NICE-defined low-intensity interventions.

Exclusion criteria: Inability to participate because of insufficient English or cognitive impairment, current major depression, comorbid anxiety disorder(s) causing greater distress than GAD, significant dependence on alcohol or illicit drugs, comorbid psychotic disorder, received antidepressants in past 8 weeks or high-intensity psychological therapy in previous 6 months and any contraindications to treatment with sertraline.

Randomisation: Consenting eligible participants randomised via an independent, web-based, computerised system.

Interventions: (1) The SSRI sertraline prescribed in therapeutic doses by the patient's general practitioner for 12 months and (2) 14 (± 2) CBT sessions delivered by high-intensity IAPT psychological therapists in accordance with a standardised manual designed for GAD.

Main outcome measures: The primary outcome was the Hospital Anxiety and Depression Scale – Anxiety component at 12 months. Secondary outcomes included measures of depression, social functioning, comorbid anxiety disorders, patient satisfaction and economic evaluation, collected by postal self-completion questionnaires.

Results: Only seven internal pilot participants were recruited against a target of 40 participants at 7 months. Far fewer potential participants were identified than anticipated from IAPT services, probably because PWPs rarely considered GAD the main treatment priority. Of those identified, three-quarters declined participation; the majority (30/45) were reluctant to consider the possibility of randomisation to medication.

Limitations: Poor recruitment was the main limiting factor, and the trial closed prematurely.

Conclusions: It is unclear how much of the recruitment difficulty was a result of conducting the trial within a psychological therapy service and how much was possibly a result of difficulty identifying participants with primary GAD.

Future work: It may be easier to answer this important question by recruiting people from primary care rather than from those already engaged in a psychological treatment service.

Trial registration: Current Controlled Trials ISCRTN14845583.

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List of abbreviations

CAG	clinical advisory group
CBT	cognitive behavioural therapy
CI	chief investigator
CONSORT	Consolidated Standards of Reporting Trials
CRN	Clinical Research Network
CSQ	Client Satisfaction Questionnaire
CTS-R	Cognitive Therapy Scale-Revised
CTU	Clinical Trials Unit
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition
EoTC	End of Therapy Checklist
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
GAD	generalised anxiety disorder
GAD-7	Generalised Anxiety Disorder-7
GP	general practitioner
HADS-A	Hospital Anxiety and Depression Scale – Anxiety component
HAM-A	Hamilton Anxiety Rating Scale
HTA	Health Technology Assessment
IAPT	Improving Access to Psychological Therapies
JRO	Joint Research Office
MHRA	Medicines and Healthcare products Regulatory Agency
MINI	Mini International Neuropsychiatric Interview
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMB	net monetary benefit
PHQ-9	Patient Health Questionnaire-9
PI	principal investigator
PPI	public and patient involvement
PWP	psychological well-being practitioner
QALY	quality-adjusted life-year
R&D	research and development
RCT	randomised controlled trial
REC	Research Ethics Committee
SAE	serious adverse event
SD	standard deviation
SNRI	serotonin–noradrenaline reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
TCC	Therapy Components Checklist
TMG	Trial Management Group
ToSCA	Trial of Sertraline versus Cognitive behaviour therapy for generalised Anxiety
TSC	Trial Steering Committee
UCL	University College London
WSAS	Work and Social Adjustment Schedule

Plain English summary

Generalised anxiety disorder (GAD) is common, distressing and can stop people leading a full life. It is often chronic and may be accompanied by depression. Current National Institute for Health and Care Excellence guidelines outline the best initial treatments, but it is not clear whether medication or psychological therapy works best for those not responding to simpler, low-intensity treatments. Both have been found to be beneficial in randomised trials but have never been directly compared, so it is unclear what to advise patients if simpler treatments have not worked. Currently the choice is left to the patient and their doctors.

We planned a randomised trial of the medication sertraline versus intensive cognitive behavioural therapy (CBT) for people with GAD that had not been responding to low-intensity psychological treatments. People scoring highly on a specific anxiety measure (Generalised Anxiety Disorder-7), despite having received a low-intensity intervention, were asked by the psychological practitioners treating them if they would consider being assessed for the trial and randomised (allocated by chance) to either medication or high-intensity CBT. We aimed to recruit via the Improving Access to Psychological Therapies services, starting with four sites in London, the south-west and central England.

Fewer potential participants were identified than expected. Most who were identified declined involvement, mainly because they did not want to risk being allocated to take medication, although some did not want any research involvement. Only seven participants were recruited in 7 months. It may be easier to answer this important question by recruiting people from primary care rather than from those already engaged in a psychological treatment service.

Scientific summary

Background

Generalised anxiety disorder (GAD) is characterised by excessive, uncontrollable and often irrational worry that interferes with daily functioning and can cause physical symptoms. It is common, but, as symptoms have to be present for at least 6 months for the diagnosis, it is often a chronic disorder when identified. It is often comorbid with depression or other anxiety or physical health disorders, worsening the prognosis. Rates of unemployment and social isolation are high, as GAD is associated with alcohol and substance misuse in an attempt by patients to relieve symptoms. People with GAD have a high number of general practitioner (GP) visits and secondary care contacts.

The most recent National Institute for Health and Care Excellence (NICE) guidelines established good evidence for the effectiveness of low-intensity psychological interventions in GAD. Step 1 interventions are usually delivered within primary care. If symptoms persist, referral to a step 2 low-intensity psychological intervention is recommended, usually facilitated by a low-intensity Improving Access to Psychological Therapies (IAPT) worker. However, a significant number of patients will not respond to these interventions and require 'stepping up' to more intensive step 3 interventions. According to NICE guidelines, the choice at step 3 is between a high-intensity psychological intervention [cognitive behavioural therapy (CBT)/applied relaxation] and a drug treatment.

The NICE Guidelines Advisory Group proposed sertraline as a first-choice pharmacological treatment, although it does not have a marketing authorisation for GAD and there are relatively few randomised trials. Nevertheless, in terms of risk of discontinuation as a result of adverse effects, sertraline was the best-tolerated antidepressant and its availability as a generic made it the most cost-effective choice.

There are a number of cognitive behavioural models of GAD. Dugas *et al.* (Dugas MJ, Gagnon F, Ladouceur R, Freeston MH. Generalized anxiety disorder: a preliminary test of a conceptual model. *Behav Res Ther* 1998;**36**:215–26) have developed a model known as the intolerance of uncertainty. This aims to help affected individuals develop beliefs about uncertainty that are less negative, rigid and pervasive. It has been tested in four published randomised clinical trials, with results indicating that it is more efficacious than waiting list control, supportive therapy and applied relaxation. This CBT model was therefore selected for this trial.

Although there is evidence of clinical effectiveness and cost-effectiveness of sertraline for GAD compared with placebo, and also of CBT compared with waiting list controls, there have been no head-to-head comparisons of sertraline [or any selective serotonin reuptake inhibitor (SSRI)] versus CBT to evaluate which treatment is more clinically effective and cost-effective. Current NICE guidelines suggest that the choice of treatment at step 3 between a pharmacological or psychological treatment should be based mainly on patient preference.

Aims and objectives

When assessing effectiveness of CBT or SSRIs for GAD, assessment of both clinical symptoms and functional impairment is important, as is assessment of outcomes for more than a few months, given that most pharmacological studies have follow-up periods of $\leq$ 12 weeks, and there is some evidence that CBT may have a protective effect against future episodes. Longer follow-up is crucial in making future recommendations, as longer-term costs of prescriptions and of the use of health-care resources are required to evaluate relative cost-effectiveness of the treatments. Our aim was to conduct a randomised controlled trial to compare the

clinical effectiveness and cost-effectiveness of a pharmacological treatment (the SSRI sertraline) prescribed at therapeutic doses, and a manualised psychological intervention (CBT) delivered by trained psychological therapists to patients with persistent GAD that had not improved with low-intensity psychological interventions as defined by NICE.

Hypothesis

We hypothesised that, in this population, CBT would lead to a greater improvement in GAD symptoms as measured by the primary outcome the Hospital Anxiety and Depression Scale – Anxiety component (HADS-A) at the 12-month follow-up than the prescription of sertraline in primary care in accordance with recommended clinical guidelines.

Primary aim

To assess clinical effectiveness at 12 months of treatment with the SSRI sertraline compared with CBT for patients with persistent GAD that had not improved with low-intensity psychological interventions.

Secondary aim

To calculate the cost-effectiveness at 12 months of treatment with sertraline compared with CBT for patients with persistent GAD that had not improved with low-intensity psychological interventions.

Objectives of internal pilot

At the recommendation of the Health Technology Assessment (HTA) programme commissioning board, we included a 12-month internal pilot with the following objectives:

1. to test and refine recruitment methods
2. to ascertain recruitment rates across pilot sites
3. to examine comorbidity between GAD, depression and other anxiety disorders
4. to ensure that the intervention could be delivered in accordance with the protocol in both arms
5. to monitor and assess follow-up rates of the completed primary outcome measure.

Methods

Recruitment was community based and linked with local IAPT services. We had four pilot sites, based in London (Camden and Islington, with Kingston) and Greenwich, Bristol, and Coventry and Warwickshire. If the internal pilot had been successful, we aimed to work with 15 sites across England in the full trial.

People not responding to step 2 low-intensity psychological interventions for their anxiety were reviewed by their low-intensity IAPT workers [psychological well-being practitioners (PWPs)]. Those scoring ≥ 10 on the Generalised Anxiety Disorder-7 (GAD-7) anxiety measure were given brief details about the trial and, if interested in possibly taking part, their permission sought for contact by the research team. The team offered them an assessment appointment and sent a full patient information sheet. With the patient's permission, their GP was contacted and asked to complete a Medical Suitability Review form to check that the patient had no known medical contraindications to sertraline if randomised to that intervention.

At baseline assessment it was checked that participants had received and understood the information sheet, and any queries had been answered. Informed consent was obtained before any trial procedures were performed. If they were happy to proceed, inclusion and exclusion criteria were checked. The Mini International Neuropsychiatric Interview (MINI) questionnaire was administered to check if participants fulfilled *Diagnostic and Statistical Manual of Mental Disorders 4th Edition* (American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders 4th Edition*. Washington, DC: American Psychiatric Association; 2000) criteria for GAD. Other significant comorbid anxiety disorders were noted, providing that the participant considered GAD their most important problem needing treatment, but comorbid major depression was an exclusion factor.

Inclusion criteria

- Age ≥ 18 years.
- Score of ≥ 10 on the GAD-7.
- Primary diagnosis of GAD diagnosed on the MINI questionnaire.
- Failure to respond to NICE-defined low-intensity interventions.

Exclusion criteria

- Inability to participate because of insufficient English or cognitive impairment.
- Current major depression.
- Comorbid anxiety disorder(s) causing greater distress.
- Significant dependence on alcohol or illicit drugs.
- Comorbid psychotic disorder.
- Receipt of antidepressants in the past 8 weeks or high-intensity psychological therapy within the past 6 months.
- Any contraindications to treatment with sertraline (including females of child-bearing potential agreeing to a pregnancy test at the assessment).

If all eligibility criteria were fulfilled, the researcher administered the Hamilton Anxiety Rating Scale (HAM-A) and asked the participant to complete baseline primary and secondary outcome measures. A copy of the completed baseline assessment form was forwarded to the chief investigator to confirm eligibility and, if confirmed, the participant was then randomised via an independent computerised service. The randomisation outcome was transmitted electronically to the trial manager, who contacted participants to inform them which treatment group they were in.

The research team also notified the patient's GP to inform them of the treatment allocation. If randomised to the medication arm, the patient was asked to make an appointment within the next 2 weeks to see their GP to discuss starting treatment with sertraline. The research team gave the relevant local IAPT services details of participants randomised to the CBT arm – the IAPT team then contacted the patient to arrange a course of treatment.

Interventions

1. Pharmacological (SSRI sertraline): potential participants were informed that sertraline, although not having current marketing authorisation for GAD, was recommended by NICE on the basis of its effectiveness in GAD clinical trials and had agreed to be prescribed this if so randomised. Sertraline was prescribed by the patient's GP in accordance with recognised clinical guidelines. GPs were asked to review these patients regularly (at least six times in 12 months) and patients were to take the medication for 1 year unless they had significant adverse effects. The GPs were given details of the suggested timing and content of these appointments with trial participants. The GP was asked to record any adverse events and both participants and GPs were asked to report any serious adverse events or suspected unexpected serious adverse reactions to the trial team.
2. Psychological (CBT): this was delivered by high-intensity therapists from local IAPT services trained to deliver 14 (± 2) 50-minute sessions of a manualised treatment developed for use in GAD, covering six treatment modules. A 2-day training course was provided for CBT therapists and their supervisors, and the supervisors had monthly expert supervision from two of the trial co-applicants in addition to the usual monthly clinical supervision given to the therapists. Procedures were agreed for a random 10% of sessions to be independently rated and reviewed for competence and adherence by an external expert.

Outcome measures

Primary outcome

The primary outcome was the HADS-A score at 12 months (this was a change from the original protocol stipulating the GAD-7, as we were unable to ask for the GAD-7 not to be routinely collected at each session in the CBT arm, which we had originally thought possible, and considered that this might be a source of potential bias).

Secondary outcomes

Secondary outcomes included HADS-A score at 3, 6 and 9 months; HAM-A score at 12 months; GAD-7 score at 6 and 12 months (all anxiety measures); Patient Health Questionnaire-9 (depression) and EuroQol-5 Dimensions, three-level version (used in health economic analysis) scores at 3, 6, 9 and 12 months; Work and Social Adjustment Scale score at 12 months (social functioning); Employment and Social Care questionnaire score (health economics) at 6 and 12 months; Client Satisfaction Questionnaire score at 3 and 12 months; and a patient preference scale score at 12 months. We planned to collect health service use data at baseline, for the preceding 6 months and at 12-month follow-up, recording GP consultations and psychotropic drug prescriptions, secondary care attendances and IAPT CBT session attendances.

Sample size calculation

Following estimates indicating standard deviations (SDs) of between 4 and 5 for the change in HADS-A scores between baseline and 12 months for both randomised conditions, we used an estimate of 5 for the SD of our outcome measure, with an additional component of variance to give an intracluster correlation coefficient of 0.02. With the conservative assumption of a cluster size of 7 and 20% for dropouts, we needed a sample size of 360 patients to detect a ('true') average difference of 2 between treatments with 90% power at $p < 0.05$ (two-sided).

Analysis

Principal analyses would have been conducted in accordance with a prespecified statistical analysis plan, finalised before database lock and conducted in accordance with the intention-to-treat principle using generalised mixed models. In the economic analysis we planned to calculate the net monetary benefit of CBT compared with sertraline for patients with persistent GAD who had not improved with step 2, low-intensity psychological interventions.

Results

Actual versus anticipated recruitment

We anticipated slow recruitment in the first 3 months of the internal pilot, but expected that this would improve as pilot sites became familiar with participant identification and recruitment processes. We had a projected total recruitment of 90 participants over the 12-month internal pilot, based on previous local IAPT data, with a target to achieve at least 70% (i.e. 63 participants at 1 year). Unfortunately, a very slow rate of recruitment meant that 7 months into the internal pilot in January 2016 we had recruited only seven participants as opposed to the projected 40, despite trying various strategies to improve recruitment rates.

Reasons for difficulties with recruitment

Fewer potential participants were identified by the PWPs than anticipated from our earlier IAPT data, and of 60 potential participants identified at screening 45 declined to participate – the majority ($n = 30$) because of reluctance to be randomised to receive medication. A further two were ineligible, two had GPs who declined to participate and four were identified after the decision had been made to close the trial.

Many PWPs described their clients being very anxious about the uncertainty of being referred and allocated to a random treatment. As a key component of GAD is worry about uncertainty, this is something we probably underestimated and illustrates the potential difficulty of recruiting participants to a randomised

controlled trial in GAD. Most potential participants identified were reluctant to consider randomisation to medication, and recruitment via a psychological therapy service was almost certainly biased towards people expecting to receive psychological therapy and therapists expecting to deliver this.

Strategies employed to improve recruitment

A number of methods were employed to attempt to improve identification of participants by PWPs. These included circulating materials to help them keep study recruitment in mind, funding lead PWPs to facilitate recruitment, meetings to discuss possible approaches to patients' queries or concerns, and database searches to identify possible cases both retrospectively and prospectively. Unfortunately, none of these resulted in improved recruitment.

Health Technology Assessment monitoring meeting

Because of poor recruitment, the funders organised a monitoring meeting in January 2016 at which the likely reasons were discussed and two possible further recruitment strategies presented: (1) a retrospective search of GP databases to identify people with anxiety/depression in primary care who might have GAD and could be approached about the trial; and (2) also identifying potential participants through a GP database search, but then assessing suitable patients for eligibility to take part in the trial and randomisation to either sertraline or high-intensity CBT within general practice without having to engage with a step 2 treatment delivered by PWPs.

The HTA programme committee was unsure about option (1) as it was seen to be an approach that would be unlikely to be generalisable within the NHS. Option (2), conducting the trial in primary care, was considered viable but a significant deviation from the original commissioning brief, and it was thought inequitable to proceed with this without reopening the application process. The decision was therefore made to close the trial prematurely.

Conclusions and recommendations

Recruiting to a head-to-head trial of medication versus high-intensity psychological therapy does not appear feasible in a psychological therapy service in which both patients and therapists are likely to be biased towards psychological therapies. An alternative strategy would be to conduct the trial within primary care, which is where initial choices are made between drug and psychological treatments. We would suggest that the HTA programme consider this option that, although not fitting directly with the NICE stepped-care model, fits more clearly with what generally happens in clinical practice.

Given the reluctance of patients to be randomised in this trial (both a reluctance to consider randomisation to the medication arm, but also because of uncertainty associated with randomisation, which people with GAD are likely to find particularly difficult) we would suggest that a naturalistic cohort patient-preference design should be considered if randomisation is not possible within primary care.

Trial registration

This trial is registered as ISCRTN14845583.

Funding

Funding for this study was provided by the HTA programme of the National Institute for Health Research.

Chapter 1 Introduction

Clinical background

Generalised anxiety disorder (GAD) is an anxiety disorder characterised by excessive, uncontrollable and often irrational worry that interferes with daily functioning and can cause physical symptoms. People with GAD often anticipate the worst and are very preoccupied with matters such as health issues, money, death, interpersonal problems or work difficulties. Typical physical symptoms include fatigue, nausea, muscle tension, palpitations or shortness of breath, difficulties concentrating and sleep difficulties, which can lead to a misdiagnosis. These symptoms must be consistent and ongoing, persisting at least 6 months, for a formal diagnosis of GAD to be made. The disorder often begins at an early age, and signs and symptoms may develop more slowly than in other anxiety disorders.

Generalised anxiety disorder is common, with a prevalence of 4.7% in the 2007 English National Psychiatric Morbidity Survey,[1] but with lower rates of identification in primary care than expected.[2] As symptoms have to have been present at least 6 months before the diagnosis can be made, it is often a chronic disorder by the time it is identified.[3] It is often comorbid with depression or other anxiety or physical health disorders, worsening the prognosis.[4] In community samples, GAD is more common than depression,[1] with higher associated health and societal costs,[5] but it has received much less attention, so establishing the most effective treatments is crucial.

Generalised anxiety disorder is often associated with significant morbidity in terms of distressing psychological and physical symptoms, and significant functional impairment.[4] The degree of disability has been described as similar to that in major depression or chronic physical illness.[6] Rates of unemployment and social isolation are high,[4] as is concomitant alcohol and substance misuse in an attempt to alleviate symptoms.[7] People with GAD have high numbers of general practitioner (GP) visits and secondary care contacts, both because of associated physical/somatic symptoms and because GAD is often comorbid with chronic physical health problems.[8]

The 2011 National Institute for Health and Care Excellence (NICE) guidelines entitled *Generalised Anxiety Disorder and Panic Disorder (With or Without Agoraphobia) in Adults: Management in Primary, Secondary and Community Care*[9] established good evidence for the effectiveness of 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 psychoeducation groups, usually facilitated by a low-intensity Improving Access to Psychological Therapies (IAPT) psychological worker].[10] However, a significant number of patients will not respond to these interventions and require 'stepping up' to more intensive step 3 interventions (*Figure 1*).

A substantial percentage of people with anxiety and/or depression referred to IAPT low-intensity workers still have high Generalised Anxiety Disorder-7 (GAD-7) questionnaire scores after receiving a step 2 intervention, indicating that they have not yet been effectively treated.[11] GAD is also potentially a long-term, relapsing condition. Thus, providing the most effective treatment, with a reduced likelihood of relapse, should provide significant benefits in terms of both individual morbidity and accompanying health and social costs to society, and was the focus of this study.

Existing research

The National Institute for Health and Care Excellence conducted a systematic review of placebo-controlled antidepressant studies in GAD.[9] Thirty-four studies were identified that were generally rated as being of

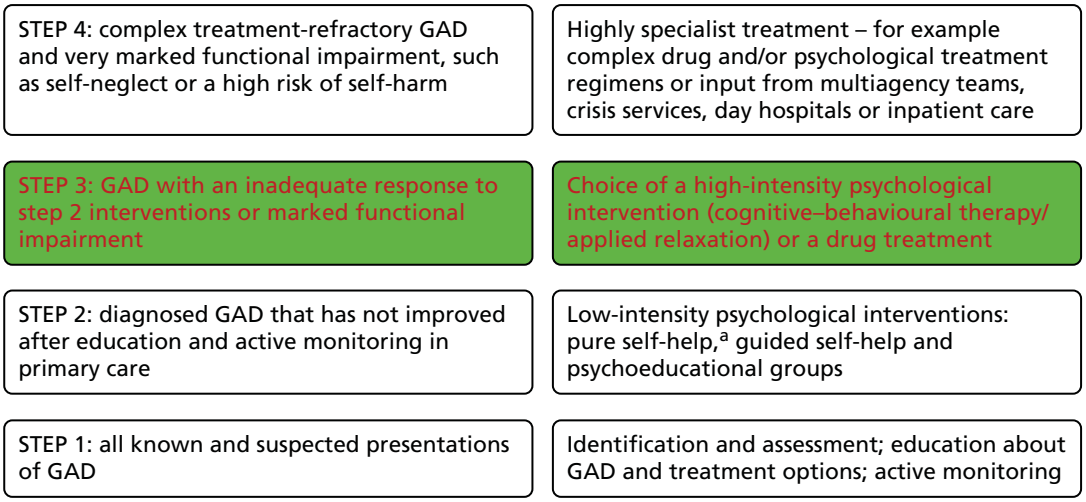


FIGURE 1 Stepped-care model for GAD. a, Pure self-help is defined as a self-administered intervention intended to treat GAD and involves self-help materials (usually a book or workbook). It is similar to guided self-help but without any contact with a health-care professional. Red font shows the step or choice of treatments that are assessed in this trial.

high quality, although relatively short in duration (8–12 weeks). Of these trials, 17 involved selective serotonin reuptake inhibitors (SSRIs), whereas 16 involved the serotonin–noradrenaline reuptake inhibitors (SNRIs) venlafaxine and duloxetine. Both of the SNRIs, as well as the SSRIs 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 Hamilton Anxiety Rating Scale (HAM-A) scores[12] and increased the probability of patients responding to treatment.

Generally, the 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.[9] There was no clear evidence of a dose–response relationship for any particular antidepressant, and the most commonly experienced side effects were nausea and insomnia. These placebo-controlled studies were generally not more than 12 weeks in duration, although GAD is considered to be a chronic disorder and guidelines recommend the continuation of treatment in responders. A meta-analysis of available relapse prevention studies suggested an important effect of continuing effective pharmacological treatment for up to 1 year in patients with GAD who have responded to pharmacological therapy,[13] although there is currently no evidence that sertraline is effective in preventing relapse.[14]

Although there is evidence of the clinical effectiveness and cost-effectiveness of sertraline for GAD compared with placebo, and also of cognitive behavioural therapy (CBT) compared with waiting 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 effective 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 if patients have such a choice in some areas.

In assessing the effectiveness of CBT or SSRIs for GAD, it is necessary to consider both 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 > 12 weeks[9] and there is some limited evidence that CBT may have a protective effect against future episodes.[15] Longer follow-up is also crucial in making future recommendations, as the longer-term costs of prescriptions and use of health-care resources associated with each type of treatment are required to evaluate their relative cost-effectiveness.

Following the updated NICE guidelines, there has been increased interest in GAD in the primary care community, but uncertainty remains regarding whether pharmacological or psychological treatment is indicated in more persistent cases.[16] Clinicians can be reluctant to prescribe the SSRI sertraline, which, although found by NICE to be the most cost-effective acute drug therapy for GAD, does not currently have marketing authorisation for this use. Clear data regarding whether the SSRI sertraline or CBT is most effective longer term in treatment of GAD, as well as further information about the safety and efficacy of sertraline in this patient group, is of direct relevance to the NHS.

The NICE committee conducted a search for relevant updates to the 2010 guideline in 2012, but no relevant trials adding to the literature were identified.[17] The authors of this report have also conducted a further rapid search of the literature to see if they could identify any relevant trials published between 2013 and early 2016, but none was found. Most of the studies continue to evaluate the effect of either CBT or medication for patients with GAD with no head-to-head comparison of a recommended psychological treatment versus pharmacotherapy. One study by Crits-Christoph *et al.*[18] combined treatment with venlafaxine with 12 sessions of CBT for patients who wished to have this and found no added benefit from the CBT at the 24-week follow-up, although the numbers in both groups were relatively small and those in the venlafaxine-only group showed quite a marked benefit from this treatment.

The National Institute for Health and Care Excellence guidelines research recommendation

The research recommendation from the NICE GAD Guidelines Group[9] suggested the following: 'A comparison of the clinical and cost-effectiveness of sertraline and CBT in people with GAD that have not responded to guided self-help and psycho-education'.

This recommendation suggested using a randomised controlled design in which people who had not responded to low-intensity step 2 interventions for GAD would be allocated openly to one of three groups: sertraline, CBT or waiting-list control for 12–16 weeks, with the control group being important to assess whether or not the two active treatments would produce effects greater than that of natural remission. It was suggested that follow-up assessments should be continued over the next 2 years to establish whether or not any short-term benefits were maintained and whether or not either active treatment produces a better long-term outcome.

Health Technology Assessment-commissioned research proposal

The research proposal commissioning brief published subsequently by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme panel in 2013 was a little different, in that it gave the following brief for the research question, omitting the third control arm to the trial and not stipulating assessment after 12–16 weeks:

> *Is a selective serotonin reuptake inhibitor (SSRI) or cognitive behavioural therapy (CBT) more clinically and cost-effective for patients with generalised anxiety disorder (GAD) who have not responded to low intensity psychological interventions recommended in a stepped-care model?*

Following from this, our final approved proposal was for a 'Randomised controlled trial of the selective serotonin reuptake inhibitor sertraline versus cognitive behavioural therapy (CBT) for anxiety symptoms in people with Generalised Anxiety Disorder (GAD) who have failed to respond to low intensity psychological interventions as defined by the NICE GAD guidelines', with the primary outcome being assessed at 12 months (see *Chapter 2*, *Methods*, for further details).

Background to the choice of interventions to be assessed

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[19,20]).[9] Nevertheless, in terms of risk of discontinuation because of adverse effects, sertraline was the best tolerated antidepressant and was available as a generic brand, making it the most cost-effective choice. Duloxetine (a 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[21] and escitalopram was still on patent and significantly more expensive at the time of submitting the proposal. There are also more concerns about it extending the QT interval, although it is recognised that sertraline can do this in vulnerable cases.[22] In the two sertraline studies in GAD, sertraline was dosed flexibly between 50 and 150 mg daily (mean dose at the end of treatment about 90 mg). In one study sertraline was started at 25 mg daily for 1 week to improve tolerance early in therapy,[23] and this acclimatisation period is also recommended by the manufacturer in the licensed use of sertraline in post-traumatic stress disorder, social anxiety disorder and panic disorder.[24]

Cognitive behavioural therapy

There are a number of cognitive behavioural models of GAD. Examples include the cognitive avoidance model,[25] the metacognitive model[26] and the emotion dysregulation model.[27] Dugas and Koerner[28] have also developed a model of GAD known as the intolerance of uncertainty model. 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.[29,30] 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,[31] and the experimental manipulation of intolerance of uncertainty leads to corresponding changes in worry and monitoring behaviour.[32,33] Thus, data from correlational, longitudinal and experimental studies suggest that intolerance of uncertainty plays a key role in GAD. The Dugas and Koerner model[28] is one of three CBT protocols for GAD, which guides IAPT services in 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 randomised clinical trials, with results showing that it is more efficacious than a waiting list control,[34,35] supportive therapy[36] and applied relaxation.[37] The findings also show that 60–77% of patients attain GAD remission and that 50–55% achieve high-end state functioning following the treatment. The CBT protocol developed by Dugas and Robichaud (i.e. based on the intolerance of uncertainty model of GAD) was therefore used in this trial.[38]

Time course of therapeutic effect and longer-term benefits

The planned comparison was between SSRI medication and CBT, which are both active treatments. However, we considered that in a pragmatic trial the time course of benefit is likely to differ. The SSRI medication might have a benefit earlier on, but it is likely that 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 CBT would continue to have benefit for the 12-month duration of the trial. As a result, our hypothesis was that CBT would lead to a better outcome than SSRIs at the 12-month follow-up point.

Chapter 2 Trial design: aims, objectives and methods

This chapter details the aims, objectives and methods of the trial as originally planned and approved by the funder, and subsequent modifications made as a result of discussions among the Trial Management Group (TMG) and with the sponsor.

Summary of proposed research

The trial was entitled the 'Randomised controlled trial of the SSRI sertraline versus CBT for anxiety symptoms in people with GAD who have failed to respond to low-intensity psychological treatments as defined by the NICE guidelines'. The trial acronym decided was ToSCA (Trial of Sertraline versus Cognitive behaviour therapy for generalised Anxiety).

Overall aim

To conduct a randomised controlled trial (RCT) to compare the clinical effectiveness and cost-effectiveness in terms of symptoms and function of a pharmacological treatment (the SSRI sertraline) prescribed at therapeutic doses, with a manualised psychological intervention (CBT) delivered by trained psychological therapists, to patients with persistent GAD that has not improved with low-intensity psychological interventions as defined by NICE.

Hypothesis

Our hypothesis was that in people with GAD who had not responded to low-intensity psychological interventions, as recommended by NICE, CBT would lead to a greater improvement in their GAD symptoms as measured by the Hospital Anxiety and Depression Scale – Anxiety component (HADS-A)[39] at the 12-month follow-up than prescription of the SSRI sertraline by their GP in accordance with recommended clinical guidelines.

Primary aim

To assess the clinical effectiveness at 12 months of treatment with the SSRI sertraline compared with CBT for patients with persistent GAD that has not improved with low-intensity psychological interventions.

Secondary aim

To calculate the cost-effectiveness at 12 months with the SSRI sertraline compared with CBT for patients with persistent GAD that has not improved with low-intensity psychological interventions.

Detailed objectives

Internal pilot (first 12 months of the recruitment period)

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 referred into the study.
4. To ensure that the intervention can be delivered in accordance with the protocol in both arms, with satisfactory delivery of training and monitoring procedures.
5. To monitor and assess follow-up rates of the completed primary outcome measure (HADS-A) at 3 and 6 months within the pilot trial.

Overall trial (whole 24 months of the recruitment period including the internal pilot)

1. To recruit sufficient eligible patients with a *Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition (DSM-IV)[40] diagnosis of GAD willing to participate.
2. To compare the effect of high-quality, reproducible pharmacological and psychological interventions delivered in accordance with clear criteria and evidence-based guidelines. We asked participating GPs to follow established clinical guidelines for delivery of the pharmacological intervention, and the psychological intervention was 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 the results in accordance with the Consolidated Standards of Reporting Trials (CONSORT) and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines.
5. To disseminate the outcomes to the NHS, academic colleagues, relevant service user groups and the wider community.

Methods

Setting

The study was community based and linked with local IAPT services.[10] We aimed to work with five recruitment sites in southern England during the pilot phase and up to 15 sites across the whole of England in the full trial.

Recruitment of participants

People who had not responded to step 2 low-intensity psychological interventions for anxiety or depression who were being considered for step 3 interventions within their local IAPT services were considered eligible (*Box 1* contains a list of step 2 low-intensity interventions meeting the inclusion criteria). Identification was by low-intensity IAPT workers, who routinely administer the GAD-7 anxiety measure[41] and Patient Health Questionnaire-9 (PHQ-9) depression measure,[42] reviewing patients. Those patients scoring ≥ 10 on the GAD-7 were given brief details about the trial and if they were interested in finding out more, and possibly taking part, their permission was sought for contact by the research team. If they were unsure about their interest at this stage they were given a brief flyer about the aims of the trial and invited to contact the research team for more information or to discuss things further.

The central research team (trial manager/research assistant) were faxed the details of those who had agreed to be contacted by the research team and aimed to respond within 1 week (preferably by telephone or e-mail or, if not, by letter) offering them an appointment at the IAPT premises or their own home, whichever was preferred. A full study information sheet was sent to potential participants at this stage (see *Appendix 1*) and the patient's GP was contacted, with their permission, and asked to complete a Medical Suitability Review form to check that there were no known medical contraindications to them being prescribed sertraline if they were randomised to that intervention arm in the trial (see *Appendix 2*).

BOX 1 ToSCA: included and excluded low-intensity step 2 interventions

A key inclusion criterion for the study is that patients should have received an initial low-intensity intervention but still have above-threshold symptoms (GAD-7 score of ≥ 10). Set out below are the types of low-intensity intervention (and the minimum number of sessions for each) that meet this inclusion criterion and also some excluded interventions.

Included interventions

- Guided self-help carried out by a PWP or equivalent low-intensity worker: patient needs to have had at least two treatment sessions after initial assessment session.
- Pure self-help (non-facilitated self-help): patient needs to have had at least one follow-up session after the self-help resource was recommended.
- cCBT: patient needs to have logged on and completed at least two cCBT sessions.
- Psychoeducational or similar group facilitated by a PWP or equivalent low-intensity worker: patient needs to have attended at least two sessions of the group.
- Exercise intervention if the exercise is for mood/anxiety: patient needs to have tried the recommended exercise intervention at least twice.
- One-off workshop lasting at least half a day, facilitated by a PWP or equivalent low-intensity worker.

Excluded interventions

- Signposting interventions (signposting to other services).
- Guided self-help carried out by a qualified (or trainee) CBT therapist or other high-intensity therapist.
- Psychoeducational or similar group, or one-off workshop facilitated by a qualified (or trainee) CBT therapist or other high-intensity therapist.

cCBT, computerised cognitive behavioural therapy; PWP, psychological well-being practitioner.

Recruitment appointment/baseline assessment

The baseline interviews and assessments were conducted by a member of the central or local research team (research assistant or clinical studies officer). They checked, at the outset, that potential participants had read and understood the study information leaflet, and answered any queries. They also checked that the patient understood the reasons for the study and confirmed at that point that they were interested in taking part on the understanding that, if randomised to the drug arm, they would receive the SSRI sertraline that, although proposed for use outwith a marketing authorisation for GAD, was recommended by NICE on the basis of its clinical effectiveness and cost-effectiveness in randomised trials. They also ensured prior to the appointment that there were no medical contraindications to receiving the medication sertraline recorded on the Medical Suitability Review form as returned by the GP (see *Recruitment of participants*, above).

Those agreeing to take part were asked to give fully informed consent before undergoing the eligibility check and baseline assessment. It was expected that most patients would be willing to consent to the study at the baseline visit, but if they were unsure they could be rescheduled for consent and baseline assessment at a later date. The assessment was conducted at the IAPT site or GP surgery in accordance with patient preference. Written consent was obtained by a delegated and appropriately trained member of staff. No clinical trial procedures, including confirmation of eligibility, were conducted prior to taking consent. A copy of the consent form was given to the patient, the original retained in the investigator site file and a further copy sent to the patient's GP for their medical notes (see *Appendix 3*).

If potential participants were happy to proceed, then the inclusion and exclusion criteria were checked (see *Inclusion criteria* and *Exclusion criteria*), which included administering a pregnancy test to females of child-bearing potential. In assessing whether or not the potential participant fulfilled the DSM-IV criteria for GAD, the relevant sections of the Mini International Neuropsychiatric Interview (MINI) questionnaire[43] were administered by the research team member (depression, panic, social anxiety, alcohol and substance misuse, and GAD). If the DSM-IV criteria for GAD were fulfilled, potential participants were asked to confirm whether their GAD or worry symptoms were more severe and of more concern to them than any symptoms that they might have associated with psychological comorbidities, such as depression and other anxiety disorders, and that this was an important problem for them that they wanted to address.

If they fulfilled this criterion and all the other eligibility criteria, the researcher then administered the HAM-A questionnaire[12] and asked the participant to complete the primary and secondary outcome measures at baseline, aiming for 100% completion of measures at baseline (see *Outcome measures*).

Inclusion criteria

- Age ≥ 18 years.
- Positive score of ≥ 10 on the GAD-7.
- Primary diagnosis of GAD as diagnosed on the MINI.
- Failure to respond to NICE-defined low-intensity interventions.

Exclusion criteria

Exclusion criteria were expanded from those in the initial approved protocol after discussion with the sponsor [University College London (UCL) Joint Research Office (JRO)].

- Inability to complete questionnaires because of 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.
- Currently on contraindicated medication: monoamine oxidase inhibitors within the past 14 days or pimozide.
- Patients with poorly controlled epilepsy.
- Known allergies to the investigational medicinal product or excipients.
- Concurrent enrolment in another investigational medicinal product trial.
- Severe hepatic impairment.
- Women who are currently pregnant or planning pregnancy, or lactating.
- Patients on anticoagulants.
- History of bleeding disorders.

Randomisation and notification of general practitioner and cognitive behavioural therapists

A copy of the completed baseline assessment form was forwarded by the researcher to the chief investigator (CI) or delegated clinician in order to confirm participant eligibility. After confirming eligibility, the CI or delegated clinician accessed a web-based interface using a unique username and password, and entered the unique study identification number for the participant in order to randomise them to one of the

two intervention arms via an independent computerised service (Sealed Envelope Ltd, London, UK) provided by the PRIMENT Clinical Trials Unit (CTU). There were no stratification variables. The randomisation outcome was transmitted electronically to the trial manager who then contacted the individual participants within 2 working days of their baseline assessment to inform them of which treatment group they were in.

The research team (trial manager or research assistant) ensured that the patient's GP was notified about their patient being enrolled in the trial and which treatment arm they were in. They were also notified if the patient was not eligible for inclusion in the trial (see *Appendix 4*).

If they had been randomised to the medication/sertraline arm, the patient was asked to make an appointment within the next 2 weeks to see their GP to discuss starting the treatment, and the research team let their GP know that they would be doing this (see *Appendix 5*).

The research team also gave the relevant local IAPT services the details of participants randomised to the CBT arm – the IAPT team then contacted the patient to arrange a course of treatment.

Interventions

Pharmacological intervention: sertraline

The medication sertraline was prescribed by the patient's GP in accordance with recognised clinical guidelines. The GPs were asked to review these patients regularly (at least six times in 12 months) and patients were to take the medication for 1 year unless they had significant adverse effects. The GPs were given details of the suggested timing and content of each of these appointments with the trial participants (see *Appendix 6*).

The GP was to act in the best interests of the participant at all times, so was free to refer them to secondary care services or psychological treatments if indicated. We explained that we would prefer patients in the SSRI arm not to be referred to or receive CBT while in the trial, but appreciated this might occasionally happen and should be documented in their GP notes.

If the patient made any interim visits to the surgery to discuss their treatment for GAD or issues to do with the medication being received, we asked for these to be clearly documented in their notes (we costed for up to four additional visits per GP to cover this possibility).

The GP was asked to record any adverse events and both the participants and their GPs were asked to report any serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs) to the trial team (see *Appendix 7*).

Psychological intervention: cognitive behavioural therapy

This was delivered by high-intensity therapists from local IAPT services who were trained to deliver 14 ($\pm$ 2) 50-minute sessions of a manualised treatment developed for use in GAD.

This covered six treatment modules:

1. Psychoeducation and worry awareness training – the first few sessions of treatment are devoted to psychoeducation in which 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 recognise 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.
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.[44]
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.[45] Written exposure sessions are continued until writing about the feared outcome no longer provokes anxiety (typically 8–10 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 encouraged to continue practising their new skills and prepare for stressors that may arise.

Sessions were to be digitally recorded and a random 10% to be assessed for quality (fidelity to the manual and therapist competence) by an independent external assessor according to prespecified criteria (see *Chapter 6* for further details).

Usual care by general practitioner

Randomisation was between sertraline prescribed by the participant's GP and CBT provided within an IAPT service, and both interventions were to be in addition to any other usual care provided by the GP. As always, the patients could be offered other medication or psychotherapy as part of their usual care, although we encouraged the GPs not to change the patient's medication unless clinically indicated or requested by the patient, and not to refer them for CBT while in the sertraline arm if possible. Usual practice would be to allow the patient with GAD to choose, with the help of their GP, between a SSRI and CBT if they met the criteria for a step 3 intervention and if neither was contraindicated.

Patients in the CBT arm were likely to receive their CBT treatment more quickly than is usual in most NHS settings, and it was a psychological intervention specifically developed for people with GAD that is not current UK practice. NHS waiting lists mean that patients in the SSRI arm who then asked to be referred for CBT were likely to experience significant delays in receiving this. We proposed to record and measure all use of antidepressants and other forms of counselling or psychotherapy, whether NHS or private, and to take account of these in the analysis.

Outcome measures

The outcome measures to be collected during the trial are summarised in *Table 1*, according to the time at which each would be collected.

Primary outcome

The primary outcome was the HADS-A measured at 12 months. This is the 7-item anxiety component of the Hospital Anxiety and Depression Scale, a very widely used 14-item scale that can be self-administered. It has high validity and reliability, and the anxiety and depression components have been assessed separately as primary outcomes.[39]

The primary outcome measure was initially the GAD-7,[41] but this was changed to the HADS-A about 6 months after the study had started and before the recruitment of any trial participants had begun. This was done because we had originally understood, when selecting the GAD-7 as our primary outcome measure for both intervention arms, that it would be possible to ask participants seeing IAPT high-intensity therapists for treatment in the CBT intervention arm not to complete the GAD-7 questionnaire at every CBT session, which is IAPT's current usual practice. Unfortunately, it was not possible to negotiate this in all the pilot study areas. As a result of this we were concerned that using the GAD-7 in the trial as the

TABLE 1 Summary of study assessments

	Time point (months)				
Assessment/measure	0	3	6	9	12
Informed consent	✓				
Establishing eligibility	✓				
Randomisation	✓				
Urine pregnancy test	✓				
MINI (relevant sections)	✓				✓
HADS-A	✓	✓	✓	✓	✓
GAD-7	✓		✓		✓
HAM-A	✓				✓
PHQ-9	✓	✓	✓	✓	✓
WSAS	✓				✓
EuroQol-5 Dimensions	✓	✓	✓	✓	✓
Health economics questionnaire: ESC questionnaire	✓		✓		✓
Patient preference rating scale	✓				✓
Treatment acceptability scale: Client Satisfaction Questionnaire		✓			✓
Health service outcomes	✓				✓

ESC, Employment and Social Care; WSAS, Work and Social Adjustment Scale.

primary variable when this is associated with treatment in one of the groups (i.e. the CBT group) was a source of potential bias, and we therefore decided to change the primary outcome measure to the HADS-A.

Secondary outcomes

These were all self-completed measures to be collected by postal questionnaire, apart from the researcher-administered MINI and health service outcomes collected from patient notes.

- HADS-A: the HADS-A was collected at baseline and then as a secondary outcome measure at 3, 6 and 9 months.[39]
- HAM-A: this is a 14-item observer-rated anxiety scale, which has been widely used, particularly in pharmacological studies.[12] It was to be administered by a member of the research team at baseline and at the 12-month follow-up.
- GAD-7: a 7-item self-completion questionnaire with very good sensitivity (89%) and specificity (82%) for GAD.[41] It is one of the core measures regularly administered by the IAPT services.[10] It was to be collected at baseline, and at 6 and 12 months.
- PHQ-9: this is a 9-item self-rate scale widely used to monitor the severity of depression.[41] It was to be collected every 3 months for the 12-month duration of the study, along with the HADS-A and EuroQol-5 Dimensions, three-level version (EQ-5D-3L).
- Work and Social Adjustment Scale (WSAS): this is a 5-item self-completion questionnaire that we planned to use to assess participants' difficulties with physical and social functioning.[46] It was to be collected at baseline and at the 12-month follow-up.
- EQ-5D-3L: a 5-item self-completion measure used to assess quality of life and calculate utility scores for quality-adjusted life-years (QALYs).[47] It was to be collected every 3 months for the 12-month duration of the study, along with the HADS-A and PHQ-9.

- Employment and Social Care questionnaire (ESC): relevant data on services used and productivity losses were to be collected using this modified version of the Client Service Receipt Inventory[48] at baseline, and at the 6- and 12-month follow-up.
- Patient acceptability measure: we planned to use the Client Satisfaction Questionnaire (CSQ), a brief 8-item self-completion questionnaire administered at 3 and 12 months.[49]
- Patient preference rating scale: we planned to use a Likert scale used by our team in other studies, also administered at baseline and at the 12-month follow-up.
- MINI:[43] it was an addition to the original protocol to also administer the MINI questionnaire at the 12-month follow-up to assess the depression, panic, social anxiety and GAD components, with the intention of establishing whether or not the participant met the criteria at follow-up for DSM-IV caseness for GAD or any of the common psychological comorbidities.
- Health service outcomes: we planned to collect health service use data from both intervention arms at baseline, capturing health service use for the preceding 6 months, and again at 12-month follow-up for the following items of health service use during the preceding 12 months: total GP consultations as well as those coded for GAD, psychotropic drug prescriptions from the GP surgeries, and secondary care attendances including mental health and psychological services. The IAPT sites agreed to inform the research team of the attendance rates for CBT sessions attended by trial participants in the CBT intervention arm.
- Serious Adverse Events Monitoring Form: we planned to use the standard SAE template provided by the PRIMENT CTU, modified for use in this study.

Final assessment at 12 months

A member of the research team would have administered the HAM-A face to face to all participants at 12 months and encouraged them to complete the 12-month outcome measures at this point to ensure optimum data collection. This would have involved a different member of the research team from the original assessor, who would have been blind to the participant's trial allocation. As a check on this, they would have been asked to say which trial arm each participant they assessed had been randomised into.

Procedures for reporting and recording serious adverse events

Patients were asked at each GP visit about side effects or health issues occurring while on medication, as is normal clinical practice, and both the patients and GPs were asked to let the study team know about any serious medical problems that may have occurred between consultations or be reported at the time of the medication review. All patients recruited to the study were given a card with details of how to contact the central research team about any serious medical problems occurring while they were in the trial at the time that they were informed about the outcome of the randomisation procedure. The same applied to both the GPs and IAPT CBT intervention therapists, who were given a brief explanatory sheet indicating when they should be informing the research team about any serious medical problem affecting a participant in the trial (see *Appendix 7*).

Both the GPs and the IAPT therapists were asked to notify the CI about any serious medical problems (to cover SAEs, SUSARs or important medical events) that might affect any participant in the trial as soon as they were aware of this. The CI or an appropriate delegated member of staff would then be asked to complete the sponsor's SAE form and to e-mail this to the PRIMENT CTU on behalf of the sponsor within 24 hours of his/her becoming aware of the event. The CI was expected to respond to any SAE queries raised by PRIMENT CTU as soon as possible. All SAEs were to be recorded in the relevant case report form and the sponsor's adverse event log, which was to be reportable to the sponsor once per year.

The CI or delegate might also contact the patient's GP, depending on the nature of the SAE, to obtain more information regarding the adverse event. All SUSARs were to be notified to the sponsor within 24 hours according to the sponsor's written standard operating procedure.

Sample size calculation

The principal outcome variable is the change from baseline to 12 months in the HADS-A score which we planned to compare between treatment groups in a regression model that accounted for baseline scores. Tests and confidence intervals for treatment effects would be based on the normal distribution – an assumption justified by the central limit theorem. Estimates for the standard deviation (SD) of HADS-A scores are available from Tyrer *et al.*[50] In this study, SDs between 4 and 5 were found for the change of score between baseline and 12 months for both randomised conditions. Therefore, we used an estimate of 5 for the SD of our outcome measure, overlaid with an additional component of variance (essentially attributable to the therapist) sufficient to give an intracluster 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, this meant we would require a total sample size of 360 patients to detect a ('true') average difference of 2 between treatments with 90% power at $p < 0.05$ (two-sided). Furthermore, the expected half-width of the 95% confidence interval for the treatment difference is then 1.2.

With this sample size, we would have retained $\geq 80\%$ power should the intraclass correlation coefficient turn out to be 0.05 rather than 0.02. Alternatively, we would retain 80% power should the SD of our outcome measure turn out to be 5.8 rather than 5. This design had the advantage of providing robust interpretation in a number of circumstances as a result of the planned precision. Thus, with no impact on alpha spending, it would be possible to interpret a significant difference between the groups of > 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 points) as demonstrating non-inferiority. Furthermore, a non-significant difference in which the outer bands of the confidence interval are < 2 points on the HADS-A would indicate equivalence. The planned precision of the trial is such that it should have provided a firm basis for decision-making even if opinions as to the correct size of the minimally important difference were to have altered somewhat before the results became available.

Statistical analysis plan

Summary of baseline data and flow of patients

We planned to follow the CONSORT guidelines in reporting and analysing our data. This included presenting a table of summary statistics for those secondary outcome variables collected at baseline showing clinical characteristics for each group along with (baseline) demographic characteristics. We also planned to create a flow chart that would provide the number of potential participants who were screened, eligible, randomised and followed up at each time point.

Primary outcome analysis

The principal outcome variable was the change from baseline to 12 months in the HADS-A score, which we aimed to compare between treatment groups in a regression model that accounted for baseline scores. Tests and confidence intervals for treatment effects would be based on the normal distribution – an assumption justified by the central limit theorem. Given that there is a single primary outcome, no corrections for multiple comparisons would be required for the statistical inference. The principal analyses would have been conducted according to a prespecified statistical analysis plan to be finalised before database lock. The principal analyses would have been conducted according to the intention-to-treat principle using generalised mixed models. The primary analysis would have used a generalised mixed model accounting for clustering of therapist effects, investigational sites (both as random effects) and a limited number of prespecified patient-level factors, including baseline HADS-A score. The principal analyses would have been based on available data, and supportive analyses would examine the extent to which the principal analyses are robust to the challenge presented by the observed loss to follow-up. Exploratory analyses would have been carried out to describe how patient preferences along with a limited number of other prespecified characteristics of participants may modify treatment effects.[50] Any subgroup analyses conducted would also have been regarded as exploratory.

Secondary outcome analysis

The secondary outcome variables would have been analysed using the same (generalised mixed model) framework as for the primary outcome variable. However, the presentation of the results would have been restricted to the confidence intervals that come out of the analysis, rather than the *p*-values.

Economic evaluation

We planned to calculate the net monetary benefit (NMB) of CBT compared with sertraline for patients with persistent GAD who had not improved with step 2 low-intensity psychological interventions. A higher NMB indicates greater relative cost-effectiveness. Health- and social-care resource use would have been collected for both interventions over the 12-month duration of the trial using patient GP records, and patients asked to complete a significantly reduced version of the Client Service Receipt Inventory (the Employment and Social Care questionnaire) at baseline and 12 months. The health service resource use data collected would have focused mostly on primary care and psychological therapies. Details of secondary care and mental health resource use would also have been collected. Health-care resource use for the preceding 6 months would have been collected at baseline for adjustment purposes only. Resource use would be multiplied by costs from nationally published sources and summed to calculate the total cost per patient. The health-care resource use associated with the interventions would have been captured in each arm as follows: the cost of sertraline 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; and training and any overhead costs.

The mean cost per patient for patients in the sertraline and CBT groups would have been calculated and confidence intervals reported, calculated using non-parametric bootstrapping with replacement and adjusting for baseline service use. The mean QALYs per patient would have been calculated from the EQ-5D-3L[51] and the UK algorithm for calculating utility scores.[52] The EQ-5D-3L would have been collected at baseline, 3, 6, 9 and 12 months to allow calculation of the area under the curve over the 12-month trial duration for the SSRI and CBT groups, adjusting for baseline differences. The NMB of both interventions would have been calculated for a range of values of willingness to pay for a QALY. Confidence intervals would have been constructed using non-parametric bootstrapping. A cost-effectiveness acceptability curve would have been used to report the probability that each intervention has the higher NMB for a range of values of willingness to pay for a QALY. One-, two- and multiway sensitivity analyses would have been conducted for any assumptions made. Missing data and clustering would have been handled as specified in the statistical analysis plan.

Sensitivity and other planned analyses

The principal analyses would have been conducted according to a prespecified statistical analysis plan, to be finalised before database lock. The principal analyses would have been based on available data and supportive analyses would have examined the extent to which the principal analyses were robust to the challenge presented by the observed loss to follow-up. Exploratory analyses would have been carried out to describe how patient preferences, along with a limited number of other prespecified characteristics of participants, might modify treatment effects.

Chapter 3 Obtaining ethics and research governance approvals

Timetable: sponsor and Medicines and Healthcare products Regulatory Agency approvals

The official start date of the trial as agreed with the NIHR's HTA programme was 1 August 2014.

This was a clinical trial of an investigational medicinal product, and we started working with the sponsor (the UCL JRO) before the official start date on the sponsorship procedures required. After several iterations the JRO approved the first version of the trial protocol on 5 November 2014 (protocol number 14/0249).

Application for clinical trials authorisation was made to the Medicines and Healthcare products Regulatory Agency (MHRA) on 7 November 2014 and their approval was received on 13 November 2014.

Ethics approval and major amendments

Our local Research Ethics Committee (REC) was Brent National Research Ethics Service Committee London, and the relevant Integrated Research Application System application was submitted to them on 7 November 2014 and presented at a meeting of the REC on 24 November 2014.

We received a favourable ethics opinion, with conditions, on 3 December 2014 and gained full approval on 9 December (REC reference number 14/LO/2105).

- Major amendment 1: at the TMG on 21 January 2015 a major protocol amendment altering the primary outcome measure from the GAD-7 to the HADS-A was suggested (see *Chapter 2*, *Methods*). This was developed and agreed with the NIHR's HTA programme and Trial Steering Committee (TSC) before being submitted to the REC and MHRA on 9 March 2015. There were also some minor study document changes submitted with this major amendment request. Approvals were obtained from the REC on 17 March 2015 and from the MHRA on 10 April 2015.
- Major amendment 2: a further major amendment was submitted on 13 April 2015 listing the four pilot sites for the trial and giving details of their principal investigators (PIs). This was approved by the REC on 23 April 2015.
- Major amendment 3: a third major amendment was submitted on 23 July 2015 applying to change the named PI at the Bristol site and was approved on 30 July 2015.
- Major amendment 4: the final major amendment was for approval for a 6-month replacement of the CI Dr Marta Buszewicz by Professor Irwin Nazareth, this amendment was submitted on 16 September 2015 and approved on 1 October 2015.

Research governance

Obtaining research governance permission proved more complicated and led to a significant delay in being able to start the trial. It was confirmed that we had submitted a full set of documents for study-wide approval on 27 January 2015, but significant delays followed while our lead Clinical Research Network (CRN) queried the governance arrangements for participating GP practices and whether or not they should be registered as individual research sites, which would have been very administratively burdensome, given that most of the planned 360 trial participants were likely to be registered at different practices.

We worked with the CRN and the Health Research Authority to develop the documents required for a generic site-specific information form, which allowed us to obtain NHS approval for the collection of health service usage data for trial participants from their GP notes without registering each general practice as a research site. This was approved by the national NIHR Coordinated System for gaining NHS Permissions (NIHR CSP) co-ordinating centre on 14 April 2015 and we finally received study-wide research and development (R&D) approval on 27 April 2015 – 3 months after initial submission of the full set of documents (see *Appendix 8*).

Having received national approval on 14 April 2015, it then took several further months to receive local assurances for all the pilot sites – the last of these was the South London assurance for Kingston and Greenwich received on 3 July 2015.

Sponsor documentation prior to site set-up visits

From February to May 2015 the trial team worked with the PRIMENT CTU on the final documentation required for the trial management file and site files prior to the site initiation visits. This included the trial monitoring plan, trial pharmacovigilance documents and training procedures, and a formal agreement between the PRIMENT CTU and the CI because a large number of sponsor responsibilities were being delegated to the CTU.

Trial database and electronic case report form development

The trial team worked over the same period with the CTU data manager and database developer to finalise the data management plan, trial database and electronic case report forms for the study. Rigorous database testing was carried out and sign-off achieved on 25 June 2015.

Monitoring processes

The PRIMENT CTU led on developing the monitoring plan. The trial monitor was John Codington of Cod Clinical Ltd, an external monitor with whom the CTU had previously worked.

The plan was for the central research site at UCL to receive a monitoring visit 3 months after being opened and for the first monitoring visit following initiation for the IAPT pilot sites to take place after five patients had been randomised at each site. Further on-site monitoring visits were to take place annually at each site.

In the event, because of very poor recruitment no monitoring visits took place.

University College London data safe haven

We worked with the UCL Information and Services Division to set up a secure storage system for any confidential data on the UCL Data Safe Haven system, although in the event we did not need to store any data there given the lack of participant recruitment and early termination of the trial.

This service provides a technical solution for storing, handling and analysing identifiable data. It has been certified to the ISO27001 information security standard[53] and conforms to the NHS Information Governance Toolkit.[54] Built using a walled garden approach, in which the data are stored, processed and managed within the security of the system, it avoids the complexity of assured end-point encryption. A file transfer mechanism enables information to be transferred into the walled garden simply and securely.

Chapter 4 Conduct of the trial: anticipated recruitment rate, Improving Access to Psychological Therapies and research staff training, and pilot site openings

Anticipated recruitment rate

To date, there have been few large-scale trials recruiting from IAPT services, and none to our knowledge that have recruited from the caseloads of low-intensity IAPT staff or that have compared psychological interventions with medication. Three of the co-applicants (JC, MS and RS) have experience of working with IAPT services as researchers, trainers and service leads. They arranged contacts between the research team and IAPT study sites to ensure local understanding of recruitment procedures and assist in troubleshooting problems, as well as arranging training and supervision of the high-intensity CBT therapists involved in delivering the intervention (see *Chapter 6* for details of the training and supervision of the high-intensity CBT therapists).

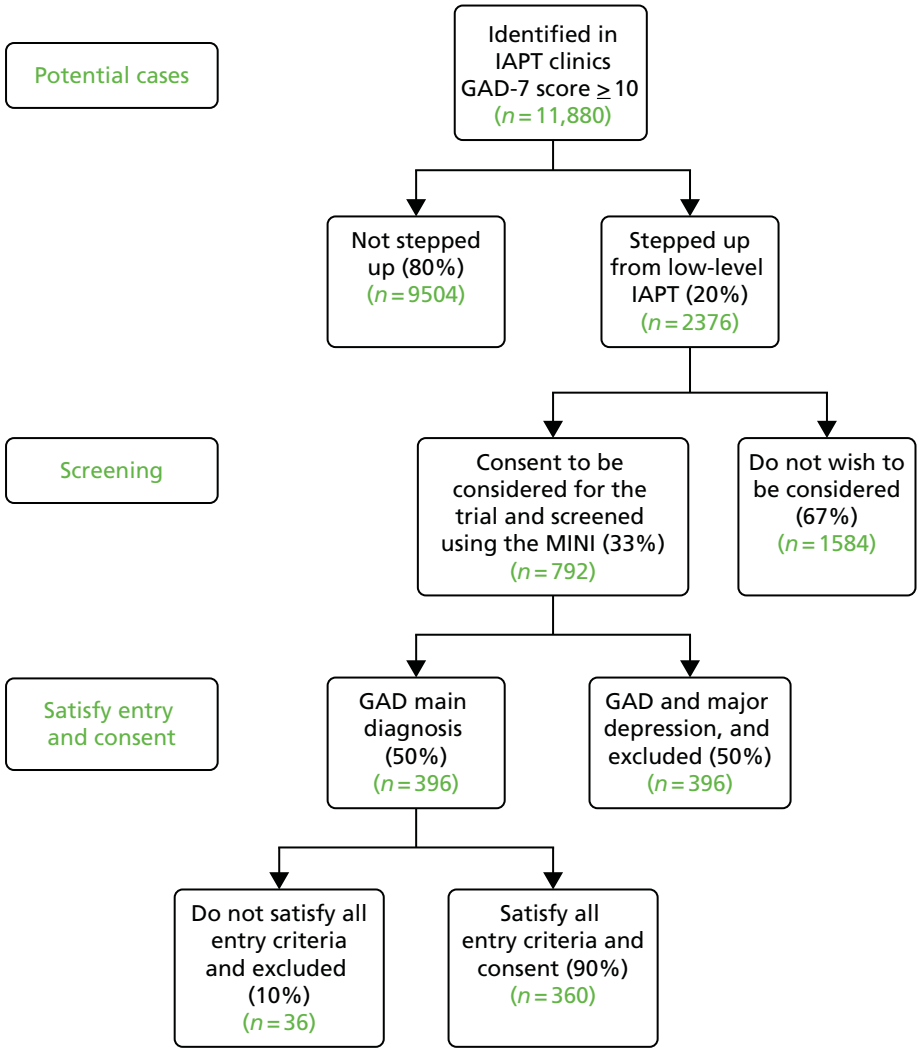
Prior to writing the proposal we examined the IAPT data for the year 2011–12 for two local London boroughs with a combined population of 426,000 during the year (Camden and Islington), among which 6569 people had an initial appointment within their IAPT services. Of these, 694 people (11%) were initially seen by an IAPT low-intensity therapist and were stepped up from a low- to high-intensity intervention with a GAD-7 score of ≥ 10. Eighty-nine (13%) of these 694 people were given a provisional primary diagnosis of GAD by the low-intensity worker and would have been potential candidates for our trial. Sixty-nine per cent were given other provisional primary diagnoses, and for 18% no diagnostic coding was made. We assumed that 67% of those with a GAD-7 score of ≥ 10 and suitable to be stepped up would be on antidepressants already or decline to be randomised. Extrapolating from the 89 people with a provisional primary diagnosis of GAD, this would have excluded 60, leaving 29 suitable and potentially willing to be randomised for the study.

As low-intensity IAPT staff have minimal training in making psychiatric diagnoses, we were conscious that a recruitment strategy that relied on them identifying people with GAD would be likely to miss many suitable people with GAD. This would include people with GAD comorbid with other anxiety disorders and with depression, pure GAD being rare compared with comorbid GAD. Accordingly, our recruitment strategy would need to encourage low-intensity IAPT staff to identify people as suitable for the study if there was a possibility they might have GAD, including comorbid with depression and other types of anxiety. So, in terms of the numbers identified in our two local London boroughs above, we wanted not just the 89 people with a GAD-7 score of ≥ 10 for whom they gave a provisional diagnosis of GAD, but all 694 people with a GAD-7 score of ≥ 10 to be considered if there was a possibility they might have GAD. We assumed that if this broader identification approach was adopted, a much larger pool of potential participants would be identified and referred for baseline assessment by the low-intensity workers, although up to half of the patients assessed for the study might then be ineligible because of a comorbid major depressive disorder or because the patient identified another anxiety disorder as being more significant than their GAD.

In order to recruit sufficient people for this trial, we needed to recruit a total of 360 people (see *Chapter 2*, *Sample size calculation*), which equated to 24 participants per study site if there were 15 sites. This would have meant recruiting one participant per site per month over the full 24 months of the trial period, or two participants per month over a 12-month period.

During our internal pilot phase we worked on forming relationships with the local low-intensity IAPT workers during the initial 3 months and ensuring that they were committed and clear as to what was required. We then aimed to recruit two participants per month from each of the five pilot sites for the succeeding 9 months, 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 also planned to consolidate our relationships with a further 10–15 sites throughout England during this time, so that we were in a good position to recruit the remaining 170 participants over the following 12 months of the main trial recruitment period.

Our assumptions regarding the number of patients to be screened and recruited across the 24 months of the whole trial are outlined in *Figure 2* and the number of patients we planned to recruit at each of the pilot sites during the 12 months of the internal pilot is given in *Table 2*. The pilot sites would continue recruiting and treating patients until the end of the full-trial recruitment period (*Figure 3*).



Assumptions made: (1) 67% of those with a GAD-7 score ≥ 10 and suitable to be stepped up will be on antidepressants already or decline to be randomised; and (2) 50% of those agreeing to be considered for the trial will be excluded because they have current major depression.

FIGURE 2 Planned screening and recruitment across the 2 years of ToSCA. GAD trial recruitment includes pilot phase.

TABLE 2 Planned recruitment rates from the four pilot sites for the first year of the trial

ToSCA IAPT pilot sites	Pilot recruitment target, *n*
Camden and Islington with Kingston	24–36
Coventry and Warwickshire	24–36
Bristol	12–18
Greenwich	12–18
Total	72–108

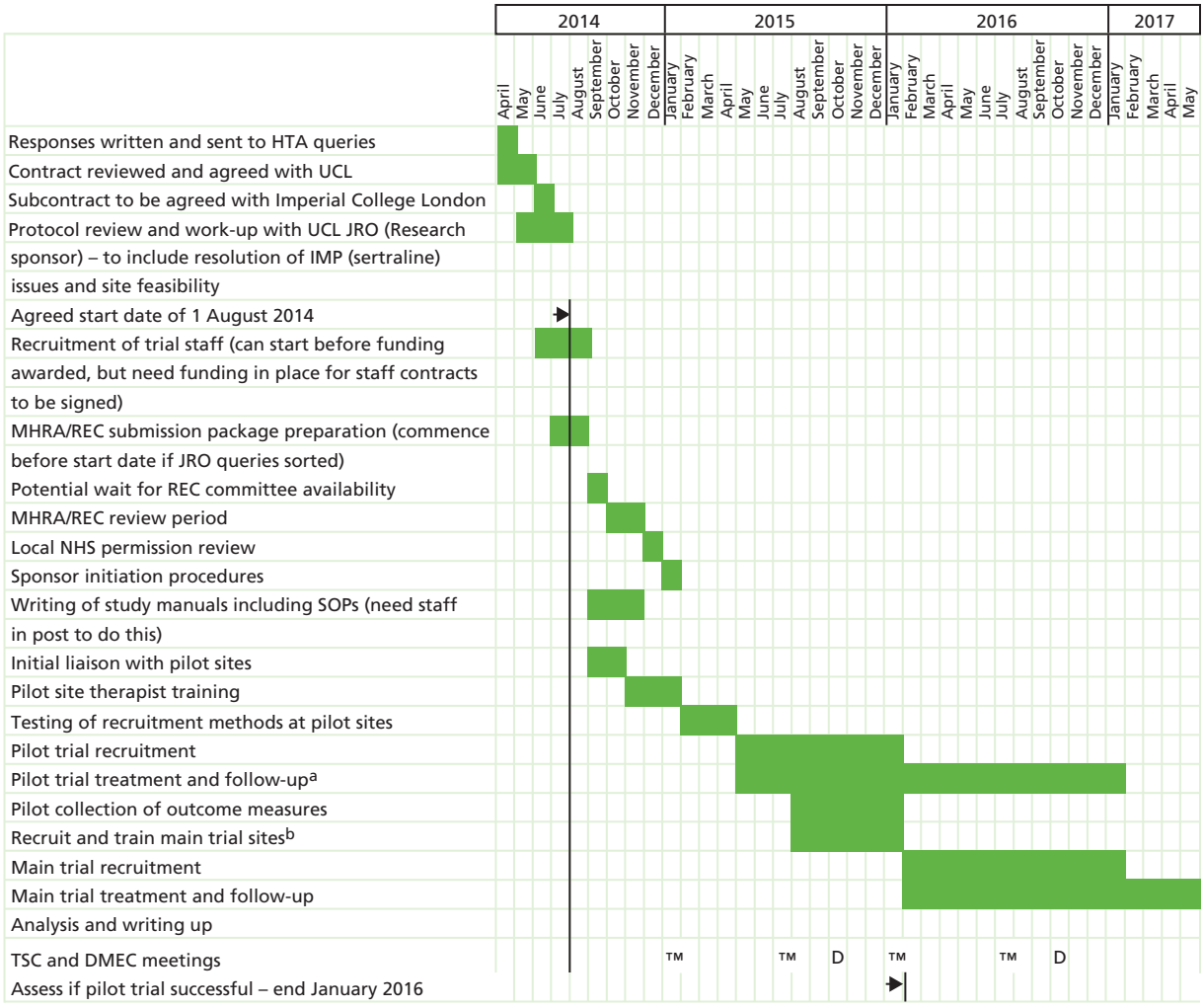


FIGURE 3 Proposed timelines for ToSCA, with a start date of 1 August 2014. a, We will offer treatment to completion to all participants recruited to the internal pilot even if not proceeding to the full trial; b, Start training therapist at the other sites in preparation for the full trial. D, Data Monitoring and Ethics Committee meeting; DMEC, Data Monitoring and Ethics Committee; IMP, investigational medicinal product; SOP, standard operating procedure; TSC, Trial Steering Committee.

In the event, we had four pilot IAPT sites in London, Central and South West England that agreed to take part at this stage and would have provided a range of populations; the London boroughs of Camden and Islington together with Kingston (all managed by the same IAPT service), Greenwich, Bristol, and Coventry and Warwickshire. Because of their relatively larger populations and IAPT service throughput, Camden and Islington with Kingston and Coventry and Warwickshire had target recruitment rates during the period of the internal pilot that were double those of Greenwich and Bristol.

The IAPT sites agreed to provide high-intensity CBT for 50% of the participants recruited. The number of therapists and supervisors trained was proportional to their target.

Because of the delays described in the previous chapter with obtaining research governance approvals as well as the sponsorship and site initiation processes (see *Chapter 3*), the first pilot site to open to recruitment was Camden and Islington with Kingston on 1 July 2015 (see *Site initiation visits, opening to recruitment and standard operating procedures* below), which was 5 months later than originally planned and meant that our 12-month internal pilot phase would have been due to end on 30 June 2016.

Trial preparation: staff training

Training of high-intensity cognitive behavioural therapists

A 2-day training session in London on 22 and 23 January 2015 was arranged for the IAPT high-intensity CBT therapists and their supervisors from each of the pilot sites, and was delivered by Professor Michel Dugas who came over from Canada to deliver the training (see *Appendix 9* and *Chapter 6*).

Liaison with and training of low-intensity psychological well-being practitioners

In preparation for each pilot site opening for recruitment, training sessions were held with the IAPT psychological well-being practitioners (PWPs) at each site. Their purpose was to prepare the PWPs for their part in identifying suitable participants for the study (see *Appendix 10*).

Training of research staff to conduct informed consent, eligibility assessment and baseline measures

Two half-day training sessions were conducted for any member of the research staff who might be involved in the baseline recruitment process – this included a combination of the research staff based at the UCL central trial office and lead PWPs or clinical studies officers involved in these procedures at the pilot sites. The first session was held on 5 May 2015 in London and included the trial co-ordinator, Dr Anastasia Kalpakidou, the Bristol Clinical Studies Officer, Joy Farrimond, and lead PWPs from Camden, Islington and Kingston (Tarun Limbachaya, Annie Ormond, Elliott Rose, Rachel Lawrence and Natalie Gunn).

The second training session was held on 16 July 2015 in Nuneaton near Coventry and included the trial co-ordinator, Dr Anastasia Kalpakidou, research assistant Sally Gascoine, ToSCA intern Alessandro Bosco and the Coventry and Warwickshire lead PWP and clinical studies officers (Helen Fletcher, James Tucker, Abayomi Shomoyei and Emily Benson).

Current good clinical practice accreditation was a condition of having a research staff role on the trial (see *Appendix 11*).

The central research team produced a full training/recruitment manual for participating sites with all the relevant questionnaires and outcome measures as appendices for reference. This was distributed in draft version to participants at the training sessions and the full electronic version sent to the pilot sites when they were open to recruitment (manual available on request).

General practitioner recruitment processes

As recruitment of patients to the trial was via the IAPT PWPs, the GPs who would potentially be taking part in the study were identified only once their patient(s) had expressed an interest in being assessed for the trial. At this point they were contacted with their patient's consent and asked to complete a Medical Suitability Review form to check that there were no known medical contraindications to them being prescribed sertraline, should they be randomised to that intervention arm in the trial (see *Appendix 2*).

In order to forewarn the local GPs and hopefully gain their co-operation with the study and a speedy response to any request for completion of the Medical Suitability Review form once requested, all the GPs in the areas where the pilot IAPT sites were situated were informed about the study in advance via their local primary care leads within their CRN structure. The procedures for this varied slightly between areas according to the procedures that they normally followed, but consisted, in essence, of an e-mail notifying the practices about ToSCA with an attached flyer (see *Appendix 12*) that informed them about the three potential procedures that they might be asked to assist with if one of their patients was recruited to the study, and the relevant rates of reimbursement per patient:

- completion of the GP Medication Suitability Review – reimbursed at £35
- prescribing sertraline for a period of 12 months or as appropriate – reimbursed at £140 in accordance with clinical guidelines (only applied to patients in the sertraline arm of the trial)
- facilitating collection of health services data at the end of the trial – reimbursed at £20.

The primary care leads of the two London CRNs involved (North Thames and South London) asked their local GPs to respond to this initial notification by sending an expression of interest in taking part in the trial, which would be the normal process for recruiting interested general practices. Very few practices responded in this way in either area, but this was not a major issue as the chances of patients being recruited to the trial from any individual practice were small.

ToSCA video

The North Central London Research Consortium, which supports primary care and mental health research in north central London where the central research site at UCL is located, also funded the production of a promotional video about ToSCA for GPs to watch. This included some educational material about GAD as well as a brief description of the background to the trial and details of the reimbursement rates for GP practices with patients involved in the trial. It was the first time this methodology had been tried.

General practices in the local area (i.e. Camden and Islington with Kingston) were reimbursed £70 if they arranged to view this video within a practice clinical meeting and could give evidence of the GPs in the practice having watched it. Ten practices were reimbursed for watching the video: seven in Camden (out of a total of 40 practices) and three in Islington (out of a total of 38 practices). Of these, all but one practice in Islington expressed an interest in taking part in the study if any of their patients were potentially eligible.

Interest was also expressed in the video by the other pilot sites where the North Central London Research Consortium was not in a position to reimburse the practices, and they were given the link to the video to watch if they wished. This has now entered the public arena via YouTube (YouTube, LLC, San Bruno, CA, USA).[55]

Site initiation visits, opening to recruitment and standard operating procedures

As described in *Chapter 3*, significant delays in obtaining research governance approval for the study as well as delays in some of the sponsorship processes meant that we were able only to start recruiting participants to the trial 5 months later than anticipated (i.e. at the beginning of July 2015 rather than 1 February 2015 as initially planned).

The central co-ordinating site based at the UCL Research Department of Primary Care and Population Health had its site initiation visit conducted by the UCL JRO on 29 May 2015 and the trial was declared open to recruitment from 1 July 2015.

The first pilot site initiation visit was at Camden and Islington with Kingston on 5 June 2015, and the site was also declared open to recruitment from 1 July 2015.

The Greenwich site initiation visit took place on 28 July 2015 and the site was declared open to recruitment on 17 August 2015.

The Coventry and Warwickshire site initiation visit took place on 29 June 2015 and the site was declared open to recruitment on 3 September 2015 (the delay between site initiation and opening to recruitment was because of discussions regarding whether or not the PI at this site might change; this was then decided against and an updating teleconference to ensure that the site was up to date with all the required procedures was held on 3 September 2015).

The Bristol site initiation visit took place on 27 August 2015 and the site was declared open to recruitment on 8 September 2015.

The research team worked with the PRIMENT CTU and the UCL JRO to identify the relevant standard operating procedures for the trial, and ensured that all relevant staff, centrally and at the pilot sites, were trained in their use and had signed the relevant registers confirming this.

Chapter 5 Participant recruitment: actual recruitment rates versus planned recruitment rate and strategies used to try and improve this

Participant recruitment to the trial

Once the sites were open to recruitment, both the screening and recruitment of trial participants was very slow. The results of screening and recruitment are summarised in *Figure 4*, the CONSORT diagram covering the time period from 1 July 2015 until 18 February 2016 following a monitoring meeting with the NIHR HTA programme, which took place on 14 January 2016 (see *Table 3* for further details).

Details of recruitment are described in *Table 3*. The first participant recruited to the trial was from Camden and Islington with Kingston, and was assessed on 29 September 2015 and randomised on 1 October 2015.

The second participant was from Greenwich, assessed on 18 November 2015 and randomised on 20 November 2015. The next three participants recruited came from Camden and Islington with Kingston (one participant), and Coventry and Warwickshire (two participants), and were randomised on 19 November 2015 and 4 and 6 January 2016. All were assessed no more than 2 working days previously – the participant randomised on 4 January 2016 had been assessed on 30 December 2015 just prior to the New Year holiday.

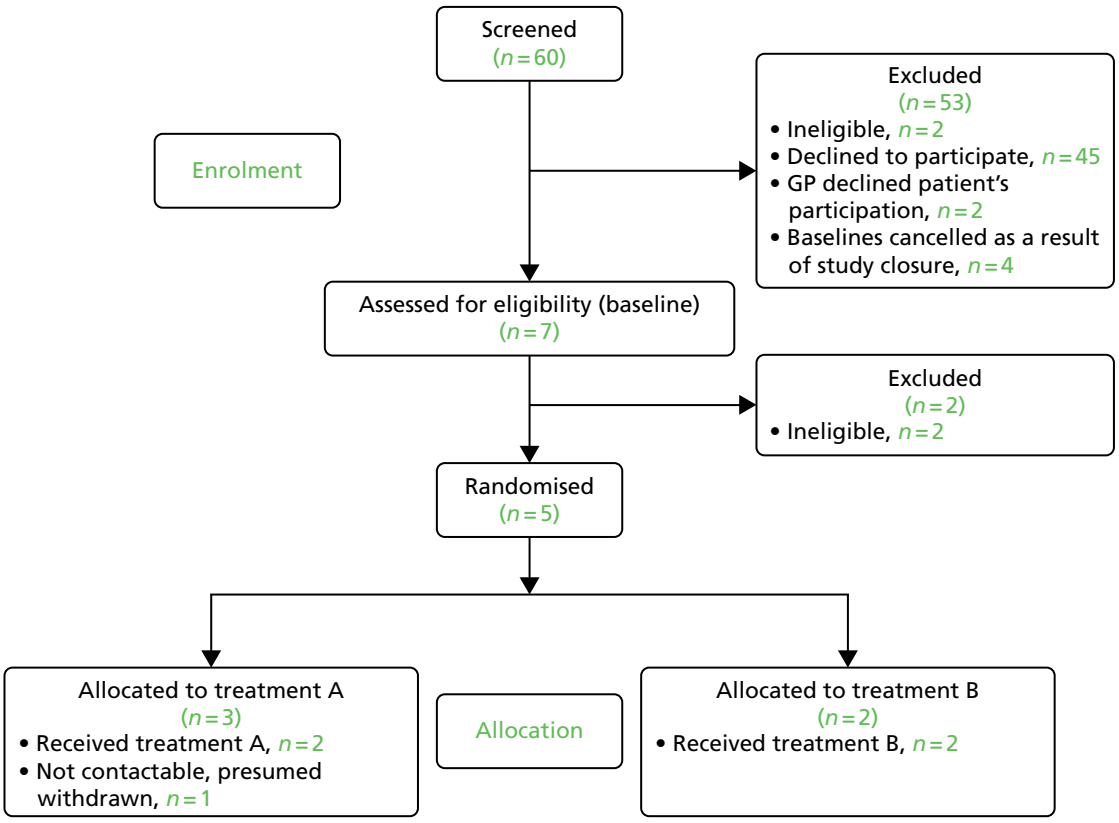


FIGURE 4 The CONSORT diagram showing participant recruitment and allocation.

TABLE 3 Screening and recruitment for ToSCA

ToSCA pilot site	Open to recruitment date	Number of identified patients	Number of dropouts	Reasons for dropouts/ uncertainty	Number of expressions of interest	Number of further dropouts/withdrawn patients	Number of completed baseline assessments	Number of scheduled baseline assessments
Camden and Islington (with Kingston)	1 July 2015	32	25		7	4/1	2 eligible	0
Camden		11	9	• Reluctant to take medication, $n = 7$ • Does not want to be involved in research, $n = 1$ • Wants CBT, $n = 1$	2	2/0 • GP was reluctant to consent, $n = 1$ • Does not want to take medication for > 6 months, $n = 1$	0	0
Islington		16	12	• Reluctant to take medication, $n = 7$ • Would like to receive CBT only, $n = 2$ • Already on SSRIs, $n = 1$ • No reason given, $n = 1$ • GAD not considered to be the clinical priority, $n = 1$	4	2/1[a] • Decided to go to GP for sertraline and also being stepped up, $n = 1$ • GP was reluctant to consent, $n = 1$	1 eligible	0
Kingston		5	4	• Reluctant to take medication, $n = 3$ • Would prefer a combination of CBT and medication, $n = 1$	1	0	1 eligible	0
Greenwich	17 August 2015	4	3	• Reluctant to take medication, $n = 2$ • Travels around the country for work, $n = 1$	1	0/0	1 eligible	0
Coventry and Warwickshire	3 September 2015	12	6	• Reluctant to take medication, $n = 4$ • Finding it hard to engage with CBT, $n = 1$ • Wants to work on specific phobia, $n = 1$	6	0/1[b]	3 (2 eligible and 1 ineligible)	Two pending baselines cancelled because of study closure

ToSCA pilot site	Open to recruitment date	Number of identified patients	Number of dropouts	Reasons for dropouts/ uncertainty	Number of expressions of interest	Number of further dropouts/withdrawn patients	Number of completed baseline assessments	Number of scheduled baseline assessments
Bristol	8 September 2015	12	6	• Reluctant to take medication, $n = 4$ • Does not want to take part in a study, $n = 1$ • Wants to have high-intensity CBT, $n = 1$	6	3/0 • Do not want to be randomised to medication, $n = 3$	1 ineligible	Two pending baselines cancelled because of study closure
Total	n/a	60	40	n/a	20	7/2	7	Four pending baselines cancelled because of study closure

n/a, not applicable.
a The patient was withdrawn from the study at Islington because of an unmet inclusion criterion (i.e. their GAD-7 score was only 5).
b The patient was withdrawn from the study at Coventry and Warwickshire because of an exclusion criterion (i.e. they were currently taking sertraline).

In addition, two potential participants were found ineligible for the trial at the baseline assessment – one from Coventry and Warwickshire assessed on 29 October 2015, who was uncertain whether or not GAD was the most important issue affecting their mental health, and one from Bristol assessed on 7 January 2016, who was excluded because they had current major depression as assessed on the MINI questionnaire.[43]

In a further two cases (both in Camden and Islington with Kingston), their GPs were not prepared to agree to have their patients in the trial or to prescribe sertraline for their GAD should they be randomised to the medication arm, so it was not possible to proceed with the baseline assessment despite the patients expressing an interest in taking part in the trial.

A little ironically, a further four potential participants identified in January 2016 (two from Coventry and Warwickshire and two from Bristol) had to have their baseline assessments cancelled following the NIHR HTA programme decision to withdraw funding from the trial (see *Chapter 8*).

Actual recruitment rates versus planned recruitment rate

We had anticipated that recruitment would be slow in the first 3 months of the internal pilot while we were testing our recruitment methods, but had expected it to improve after this as the pilot sites became familiar with participant identification and recruitment processes. In our submitted key progress figures we indicated that we expected to recruit two participants in the first month, three in the second, four in the third, five in the fourth and then 10 participants in each of the following 8 months – resulting in an anticipated total recruitment of 90 participants over the 12-month period of the internal pilot. We had an internal pilot target to achieve at least 70% of this (i.e. 63 participants recruited at 1 year).

The very slow rate of recruitment to the trial unfortunately meant that at the end of January 2016, 7 months into the internal pilot, we had recruited only seven participants, as opposed to the projected 40 anticipated (*Figure 5*). This was despite trying a variety of strategies to improve the recruitment rates, as described in following sections.

Reasons for difficulties with recruitment

The most noticeable factor was that we had fewer potential participants identified by the PWPs than we had anticipated from our earlier data, and of the 60 potential participants identified at screening, 45 declined to participate – the majority ($n = 30$) because of their reluctance to be randomised to medication, with a further person not wishing to take medication for > 6 months. Four people only wanted CBT, one wanted a combination of antidepressants and CBT, and one went to their GP to obtain this. One person was already on medication (SSRIs), one had found it hard to engage with CBT, two did not think that their GAD was their main clinical priority, two did not want to take part in research, one did not give any reason for not taking part and one travelled extensively and, hence, could not keep regular clinical appointments as would have been expected with participation in the trial (see *Chapter 8*).

The research team worked hard to try and address all the possible factors contributing to this lower than anticipated identification rate, detailed in the next section.

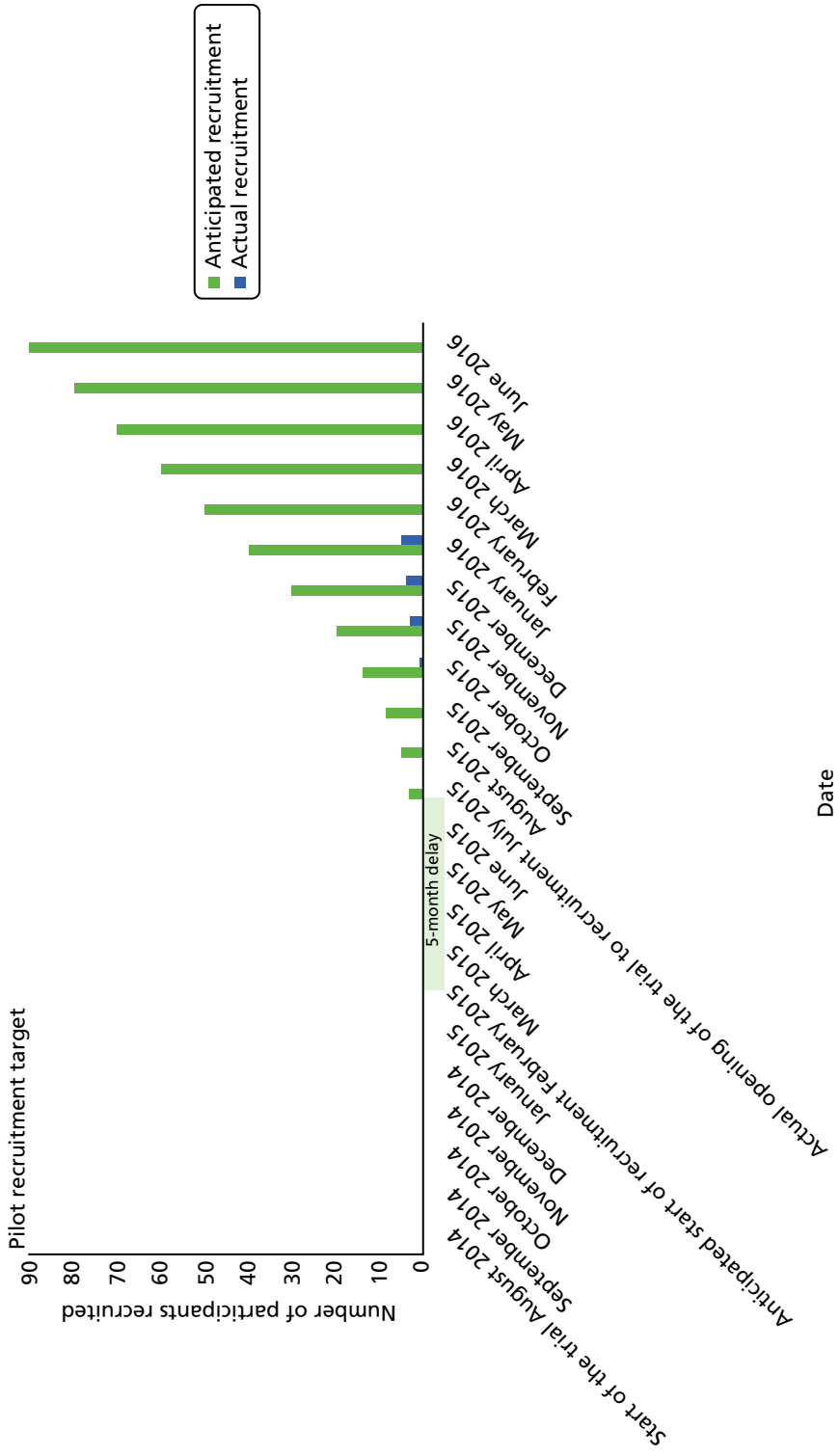


FIGURE 5 Graph showing ToSCA actual recruitment against anticipated recruitment.

Methods aiming to improve recruitment via psychological well-being practitioners

As soon as the research team became aware of the difficulties with participant recruitment, a number of methods were used to attempt to improve recruitment of participants by PWPs. These included:

- materials to help the PWPs keep in mind the study and recruitment
- funding of lead PWPs to facilitate recruitment
- reminders to PWPs about the study
- meetings with PWPs about the study
- database searches to identify possible cases.

Various materials were distributed to PWPs to serve as reminders of the study and recruitment processes. A flow chart on a single sheet set out the recruitment criteria, key points to discuss with possible eligible participants, what to do if participants agreed to be contacted by the research team or were unsure, and the logging of the outcome of these discussions. Copies of this were posted at PWPs' work stations (*Figure 6*) and in the materials PWPs took with them to clinics.

In addition, each site had one or more PWPs who were part-funded from local R&D funds to help with recruitment and baseline assessments. These PWPs were embedded in their local IAPT services as they worked clinically as PWPs in their service as well as having dedicated funded sessions to facilitate recruitment. On a day-to-day basis they liaised with their PWP colleagues, reminding them of the study both individually and in team meetings, and giving advice regarding recruitment. Several sites used the PWP case management supervision sessions to consider suggesting assessment for the trial to patients likely to have GAD at their 4-week review.

To monitor recruitment, the lead PWPs completed log sheets of potentially eligible participants and the outcome of the PWP discussions with potential participants about the study. These were to be returned fortnightly to the research team. The routine of requesting these to be returned each fortnight and prompting if log sheets had not been returned served as a repeated reminder about the study and also gave them the opportunity to enquire about any issues regarding recruitment.

In some sites, the local PI and/or members of the study research team attended routine PWP team meetings to remind them about the study and problem-solve issues regarding recruitment. As the study progressed, and it became evident that there were greater than anticipated barriers to recruitment, the

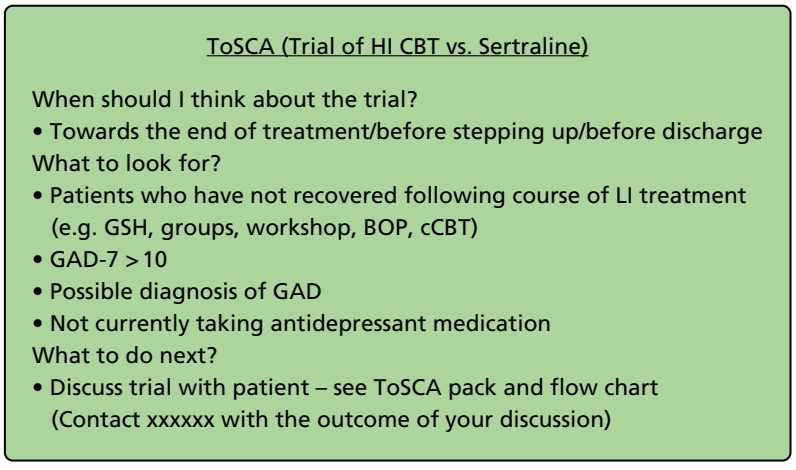


FIGURE 6 Example of reminder for PWPs attached to their monitors in Camden and Islington. BOP, books on prescription; cCBT, computerised cognitive behavioural therapy; GSH, guided self-help; HI, high intensity; LI, low intensity.

focus of these discussions was on identifying barriers that the PWPs might have in raising the study with potentially eligible participants or in pursuing these discussions in a sufficiently facilitative manner.

There were some common themes that emerged that may have contributed to the relatively low levels of identification of potential participants by the PWPs and that may be worth considering when planning future studies involving IAPT services.

Reasons given by psychological well-being practitioners for the difficulty recruiting participants to ToSCA

- We explained to the PWPs in both the written materials and face-to-face training the importance of having equipoise in explaining the trial to potential participants, and that it was an important unanswered clinical question whether CBT or medication would be the most effective treatment for these patients. However, the fact that they had been trained to deliver a low-intensity CBT intervention is likely to have given them both an overt and also less conscious bias towards psychological therapy treatments.
- A number of PWPs said that they thought many patients they saw were against trying psychotropic medication. This was backed up by many of the documented patient responses to being told about the trial, but it was unclear if the patients may have been influenced in this by the PWPs. We gave the PWPs examples of answers to give to patients who might have been concerned about the side effects of medication (*Box 2*).
- Several PWPs were concerned that patients would not be offered CBT after trying medication if the medication proved unhelpful, possibly indicating a greater enthusiasm for psychological therapy.
- Some PWPs said they thought GAD was not as prevalent in the clinical population as generally believed and that, in their experience, GAD presentations are often not the focus of psychological treatment.
- Quite a few PWPs wanted to be certain that people they discussed the trial with had GAD, although we had stated that this was not possible at their stage in the process and that we would like them to offer the possibility of the trial to anyone with a reasonable likelihood of GAD, as they would then need to be assessed using the gold standard MINI questionnaire. The PWPs said they were concerned about wasting clients' time if they did not have GAD.
- Time pressures were a virtually universal problem – all the PWPs had significant clinical caseloads and found it difficult to keep the trial in mind.
- Many PWPs reported that their clients were very anxious about the uncertainty of being referred and allocated to a random treatment. Given that their key problem is likely to have been GAD, with a core component being worry about uncertainty, this illustrates the potential difficulty of recruiting participants to a RCT in GAD. When this barrier was identified, PWPs were encouraged to suggest to potential participants that they meet with the researcher and address their questions to the researcher, rather than the PWP attempting to answer them.
- This problem with worry about uncertainty also made the PWPs concerned about making their patients more anxious when discussing the trial, with implications for their workload, as well as concern for the well-being of their patients.

A further unanticipated barrier identified through these discussions was that the supervisors of the PWPs often considered that a comorbid problem which the patient had, either diagnostic (e.g. social anxiety) or psychosocial (e.g. debt problems or relationship difficulties), was the key clinical issue to address and would direct the PWP to refer the patient for an intervention addressing this problem which meant they were not considered for the study. When this barrier was identified, local PIs and the study team encouraged PWPs and supervisors to refer such patients for a ToSCA baseline assessment where the suitability of treatment for GAD would be addressed rather than pre-empting this.

BOX 2 Suggested PWP script if patient is concerned about being randomised to medication

If the potential participant is not keen to take part in the trial because of concerns about being randomised/allocated to the medication arm, it's suggested that you ask them if they could say what it is about the medication that concerns them and see if this can be briefly discussed. The following are some common preconceptions about antidepressant medication such as the SSRI sertraline.

(a) That they will be addictive: there is no evidence of any physical addiction with a medication like sertraline, although it is better to stop it gradually rather than suddenly.
(b) That they will make people feel like 'zombies' and not themselves: again, there is no evidence of this. People do sometimes experience mild side effects when starting sertraline, such as nausea, dizziness and tiredness, but these are usually mild and short lasting, and sertraline has been prescribed in millions of doses worldwide with a very good safety profile.
(c) Sertraline has been shown in trials to be effective for GAD; what we do not know is whether it's more or less effective than the psychological CBT treatment also being offered.

You could then see if the patient feels their concerns have been addressed and they are happy to consider being in the trial, if eligible, or if they still feel clear that they do not want to do this.

IAPTUS database searches

Two months into recruitment at the first site in Camden and Islington with Kingston, there was a pilot of using the routine service clinical database (IAPTUS; adult version, Mayden, Bath) to identify potential cases. Two types of case identification method were piloted: a retrospective and prospective method.

For both methods it was staff at the pilot site (the lead PWPs) who conducted the searches.

Retrospective database searches

The retrospective method was initially used to identify cases potentially meeting study criteria, who had been discharged from low-intensity PWP treatment and stepped up to be awaiting high-intensity CBT within the service. It did not prove to be very useful in terms of identifying potential participants for the trial as, of the 18 patients who had been referred for stepping up who still had a GAD score of ≥ 10, nine had depression as their main problem, two had other clinical problems they wanted to address, one had moved, one dropped out, two declined as they did not want medication and three did not respond. There were also 14 patients who had been discharged from the IAPT service despite still having a GAD score of ≥ 10, of whom six reported having other clinical presentations as their main problem, one declined when contacted about the study and seven did not respond.

Following on from this, we examined the participant flow for the whole trial recruitment period retrospectively and this indicated a significant number of people who might have been suitable to approach to discuss assessment for participation in the trial who had not been identified by the PWPs. Using the IAPTUS database, the flow of people with GAD-7 scores of ≥ 10 during the active study recruitment period was analysed at the IAPT pilot site covering the same two local London boroughs used to estimate likely recruitment flows in 2011–12 before the trial (i.e. Camden and Islington with Kingston). Approximately 1 in 4 people assessed for treatment with a GAD-7 score of ≥ 10 were seen for at least three sessions of a low-intensity treatment (the other three out of four people either went straight to high-intensity CBT or were discharged, referred on or dropped out before having two low-intensity treatment sessions). Of those who completed at least three sessions of a low-intensity intervention, 37% were being a prescribed a psychotropic medication (data missing on a further 2%), and 50% of those who were not prescribed medication improved and had GAD-7 scores of < 10 at the end of their low-intensity treatment. All of these therefore did not meet criteria for inclusion in the study.

Of those patients who were not on medication and had not recovered, a proportion dropped out of treatment before the end of their low-intensity intervention and would not have been able to be approached by their low-intensity worker about the study. However, of those who remained potentially approachable to discuss the trial, approximately only 1 in 6 had been identified to the study team as having been approached about the study by their low-intensity worker/PWP. Unfortunately, following a change in the clinical database used by the IAPT service, the completion of diagnostic coding during the recruitment period was poor (only 28% of people with GAD-7 scores of $\geq$ 10 had primary diagnoses coded on the system) and so we were unable to use this to calculate how many of the potentially eligible and approachable patients were considered by their IAPT low-intensity worker to have a primary diagnosis of GAD rather than other diagnoses.

Prospective database searches

The prospective identification method was used to identify cases potentially meeting the study criteria who had already had three or more sessions of PWP treatment and were still in treatment with a PWP. It was instituted on a regular basis at the Camden and Islington with Kingston site, and the algorithms and methods were disseminated to the other pilot sites. On a regular fortnightly basis, cases were extracted from the IAPTUS database that met the following criteria:

1. most recent GAD-7 score of $\geq$ 10
2. seen three or more times in a step 2 treatment (could include the PWP assessment session)
3. still in a step 2 treatment
4. not on a psychotropic medication.

An e-mail was sent to the PWP treating each patient identified through these searches, giving the patient's identification details, noting that the patient was potentially eligible for ToSCA and asking the PWP to e-mail, by return, if there was some reason that they were not eligible for the study (e.g. that the patient had an agreed diagnosis or diagnoses other than GAD).

In addition, a note was placed on the front page of the patient's electronic records in IAPTUS (on the page that first comes up when the patient's records are entered) that the patient was potentially eligible for ToSCA.

Using the standard IAPTUS search to identify people at step 2 who had a diagnosis of GAD highlighted a problem that people had not always been given an accurate provisional diagnosis. In order to identify potentially eligible participants, this involved checking clinical records for GAD scores, session number and medication use.

General practitioner factors affecting participant recruitment

As the trial participants were being recruited via the IAPT service and not their GPs, we were relying on their GPs agreeing to support the trial in terms of checking their patient's medical suitability for the trial and agreeing to prescribe sertraline for those randomised to the medication arm once the patients had expressed an interest in taking part. We sent information to all the local GPs about the potential benefits of the trial for their patients, and the trial procedures and rates of reimbursement that would affect them via the local primary care research networks before the trial opened (see *Chapter 2*, *Methods*).

Thirteen GPs were approached with patient consent to complete Medication Suitability Review forms (i.e. for the five randomised participants, the two participants found to be ineligible at the baseline assessment and four participants whose baseline assessments were cancelled because the trial was terminated). Two GPs refused to complete the form for their patients.

Eleven GPs therefore completed the form and returned it. Of the two GPs who were not happy to do so, one considered that their patient had current physical problems that would make it inappropriate for them to take part in the trial despite the patient wanting to participate and the other GP simply refused to have any involvement. The research team attempted to contact both GPs to discuss the issues with them but without success.

Given the design of the study we did not consider there were any other strategies that might have allowed these two patients to participate, although they were disappointed to be excluded.

Feedback from study participants

As the trial was terminated prematurely we had only collected data at the 3-month time point from one participant and did not have a meaningful number of data to analyse. The five participants who had been recruited to the trial were all sent written notification that the study was finishing early but that we had made arrangements with their GPs or IAPT therapists to continue providing them with the intervention to which they had been randomised. The research team also contacted the participants in person to check that they had understood the implications of the trial finishing early and to get their feedback about participating in the trial in lieu of any formal results.

Out of the five randomised participants, four were spoken to via either telephone or e-mail.

1. Sertraline 1 (by telephone): was glad to have taken part. Had a positive response in terms of mood, but switched to citalopram the week of being contacted as a result of side effects.
2. Sertraline 2 (by e-mail): reported that everything is going well with the treatment.
3. Sertraline 3 (unable to contact): participant was presumed to have withdrawn/dropped out.
4. CBT 1 (by e-mail): travelling so unaware of trial closure. Was sorry that the trial was closing – reported that it had been a 'really positive experience' and offered to provide more specific feedback if necessary.
5. CBT 2 (by telephone): treatment ongoing. Felt very disappointed when the trial closed, which had a negative effect on mood. Still very anxious in general and unsure when the CBT treatment will end. Appreciated the follow-up call as they wanted to be able to give their views about the study closure.

Chapter 6 Cognitive behavioural therapy subgroup, cognitive behavioural therapy measures of competence and adherence, training and supervision of high-intensity therapists, and validation of tapes

Cognitive behavioural therapy subgroup

A CBT subgroup comprising Michel Dugas, Roz Shafran, Marc Serfaty, John Cape and Marta Buszewicz met by teleconference every 2 months during the study to discuss and confirm the procedures regarding delivery of the CBT intervention, as well as the processes for the assessment of therapist competence and adherence. This was also an opportunity for the group to discuss any issues that had come up in the expert supervision of the pilot site supervisors by Michel Dugas and Roz Shafran, and to keep the group informed about any general trial issues of relevance.

Background to cognitive behavioural therapy measures of competence and adherence

Lichstein *et al.*[56] described three important elements when evaluating CBT: first, whether or not a treatment was delivered by the therapist in accordance with the intervention model; second, whether or not there was 'receipt' by the patient (i.e. had it been understood); and, third, whether or not enactment had occurred (i.e. had the patient carried out the prescribed treatment). The parallel elements in the drug arm of ToSCA would be whether or not sertraline had been properly prescribed, whether or not the patient had understood how to take the medication (collected the prescription, understood the timing, dose, etc.) and whether or not they had actually taken the medication.

There are two main issues that were considered when deciding how to rate the CBT therapy delivered in this trial: first, did the therapist adhere to the Dugas Therapists' Manual (see *Appendix 13*) by delivering interventions specified for the treatment of GAD (adherence); and, second, was the approach to delivering the therapy of a sufficiently high standard to be considered competently delivered (competence)?

Assessment of adherence and competence is required to make sure that the trial is testing the intervention as it was designed to be delivered. In effectiveness studies, such as the current one, it can be more difficult to ensure adherence and competence because of the challenges inherent in delivering the treatment in routine clinical services. To maximise adherence and competence to the protocol, therapists must be trained and closely supervised. Within IAPT services all qualified therapists are accredited by the professional organisation, the British Association of Behavioural and Cognitive Psychotherapy. This accreditation is not in itself sufficient assurance that the specific protocol for the treatment of GAD selected for this trial will be delivered with high levels of adherence and competence. Some of the therapists and supervisors may not have been trained to deliver the Dugas model[37] but others might, and ensuring that all the therapists were able to deliver the protocol competently, and that the supervisors were able to supervise the delivery of the protocol within the clinical service, were key components of the study. The Dugas model was selected as the CBT protocol of choice because of the data supporting its efficacy as well as availability of training materials.[57]

Assessment of competence

A scale for measuring therapist competence in cognitive therapy, based on the original Cognitive Therapy Scale,[58] is the 12-item Cognitive Therapy Scale-Revised (CTS-R).[59] This revised version improves on the original Cognitive Therapy Scale by eliminating the overlap between items, improves on the scaling system and defines items more clearly. In this trial we planned to have an independent rater listening to audio-recordings of therapy sessions using the CTS-R.

Scoring

The CTS-R consists of 12 items: agenda-setting and adherence; feedback; collaboration; pacing and efficient use of time; interpersonal effectiveness; eliciting of appropriate emotional expression; eliciting key cognitions; eliciting and planning behaviours; guided discovery; conceptual integration; application of change methods; and homework setting. The CTS-R is more specific than the original Cognitive Therapy Scale in that therapist competence is defined very precisely. Each item is rated from 0 to 6 on a visual analogue scale ranging from incompetent, through to novice, advanced beginner, competent, proficient and expert. The total score ranges between 0 and 72, with a minimum score of 36 taken as competency for the delivery of therapy.

Assessment of adherence

In this context we defined therapist adherence as the extent to which the therapist stuck to the essential elements described within the treatment manual.

We aimed to collect detailed information about the content of the intervention using a Therapy Components Checklist (TCC), which was developed for use in the trial. The TCC summarises five main interventions described in the Dugas treatment manual (see *Appendix 13*) and deemed essential for successful treatment. Each of these areas is made up of a number of elements:

1. psychoeducation and worry work (three elements)
2. evaluation of the usefulness of worry (two elements)
3. uncertainty recognition/exposure (three elements)
4. problem-solving (three elements)
5. written exposure (five elements).

The TCC also includes sections about general therapy procedures (10 elements) and the specific materials used (nine elements). We also aimed to collect information about a number of interventions that are not permitted and, if used, to assess deviations from the protocol (e.g. use of controlled worry periods). There is one TCC completed per patient and the therapist reports which components were addressed after each therapy session. A more detailed description of these can be seen by referring to the TCC (see *Appendix 14*). The TCC was used in supervision, but not shared with the patient.

At the very end of a course of therapy, up to 16 sessions, the main elements of the treatment delivered are summarised in the brief End of Therapy Checklist (EoTC) (see *Appendix 15*) completed by the therapist. This consists of the same five main areas/interventions detailed above. The EoTC was not used in supervision or therapy, but solely for the purpose of assessing adherence. This was also developed by the CBT group for use in the trial.

Defining 'sufficient' adherence

The degree of adherence was rated using the EoTC as follows:

- 0 – non-adherent (between zero and two out of the five components delivered on the EoTC, i.e. < 40% of the session was spent using methods from the protocol; the rest of the time was spent on methods not in the protocol or generic techniques, such as empathic listening)

- 1 – somewhat adherent (two or three out of the five components delivered on the EoTC, i.e. 40–59% of the session was spent using methods from the protocol; the rest of the time was spent on methods not in the protocol or generic techniques)
- 2 – mostly adherent (three or four out of the five components delivered on the EoTC, i.e. 60–79% of the session was spent using methods from the protocol; the rest of the time was spent on methods not in the protocol or generic techniques)
- 3 – fully adherent (at least four out of the five components delivered on by the EoTC, i.e. $\geq$ 80% of the session was spent using methods from the protocol; the rest of the time was spent on methods not in the protocol or generic techniques).

Data collection

Therapists' ratings of adherence

The therapists would have been asked to complete (1) the TCC at the end of every therapy session as well as (2) summarising the treatment delivered during a course of therapy using the EoTC.

Independent ratings of adherence

An independent rater would have been asked to listen to all of the audio-recordings available on a patient who had completed therapy and objectively rate adherence using the EoTC, giving a score generated by adding all of the items rated as adhered to on a scale. A representative sample through random selection of 10% of all the patients can be selected and an EoTC completed for each patient. An average score can then be generated to see if the study complied with the goal of ensuring that treatment delivery was at least mostly adherent to the protocol using the method set out above.

Training and supervision arrangements for ToSCA

Training workshop

Training for ToSCA consisted of a 2-day workshop, on 22 and 23 January 2015, led by Professor Michel Dugas, who developed the CBT intervention being used in this trial and has conducted previous trials in GAD.

Attendees included the CI (MB), co-applicants from the project who are experienced CBT therapists (RS, MS and JC) and staff from the IAPT pilot centres located in south-east England – London (Camden, Islington, Greenwich), Surrey (Kingston), the Midlands (Coventry, Warwickshire) and the west of England (Bristol). The IAPT staff at each of these sites were very enthusiastic about the opportunity to receive training from Michel Dugas and places had to be limited to two therapists and one supervisor for each single pilot site (i.e. Greenwich and Bristol) and four therapists and two supervisors for the sites committed to a double recruitment figure (i.e. Camden and Islington with Kingston, and Coventry and Warwickshire) (see *Appendix 9*).

The training was delivered as a workshop, with scenarios in which attendees were encouraged to get into groups and practise using role play. It was based on the manual provided by Michel Dugas, and each therapist and supervisor was given a copy for use in the trial (see *Appendix 13*).

Plan to ensure therapist competence

All attendees met at the end of training on the final day to discuss implementation issues at their local sites. The plan was for each therapist who was going to be involved in ToSCA to treat two patients who had already been identified as having GAD within the IAPT service, using the manualised intervention that they had been trained in using by Michel Dugas. These patients would be used to help therapists and supervisors become familiar with the protocol, and optimise adherence and competence for the main trial. As these patients had not been recruited or consented to take part in the trial, it was not possible for the tapes or transcripts of their therapy sessions to be made available to the external supervisors. The local

supervisors brought any particular issues arising from the treatment of these patients to their 'supervision of supervision' sessions provided by Michel Dugas and Roz Shafran. We have termed the patients treated in this way 'practice patients', in order to distinguish them from patients who were recruited for the internal pilot who underwent a rigorous eligibility and consent process.

It was agreed that in the practice patient stage the therapists would need to treat at least two patients and the supervisors would rate the therapist on at least one session using the CTS-R.[60] It was agreed that the therapists would need to have achieved a score of ≥ 36 to be considered competent and be permitted to treat patients in the trial. A minimum score of 36 is the standard criterion for competence within IAPT services. It was intended that competence in the delivery of CBT for the main trial would be assessed in the same way (i.e. a score of ≥ 36 according to the CTS-R). In the main trial, it was intended that an expert rater (Melissa Robichaud) would independently rate 10% of all therapy sessions using the CTS-R to establish that the protocol had been delivered competently. In the unlikely event that the therapy had not been delivered with competence or adherence to the protocol, this would have been reported.

Plan to ensure therapist adherence

Adherence to the protocol is a critical part of any trial. We therefore developed a measure of adherence to the protocol for use in the main trial. The practice patient stage enabled us to test the feasibility of this measure. As described in *Assessment of adherence*, the TCC is intended to be completed after every session by the therapist to record the main content of the session, and the EoTC is designed to be completed at the end of the course of therapy by the therapist. The therapists were asked to bring the TCC completed on their 'practice patients' to their supervision sessions so that the local supervisors could help them maintain adherence to the protocol.

We planned to also use the TCC in the main trial to assess adherence, in addition to external assessment of adherence to the protocol by an expert rater (Melissa Robichaud), who had agreed to rate 10% of the sessions selected at random to ensure that the therapists had adhered to the protocol. The intention was for the external rater to listen to 10% of the sessions selected at random and rate them for adherence and competence simultaneously. We planned to examine the relationship between therapist self-ratings of adherence and external expert ratings of adherence. If there was a strong and positive relationship between the ratings, we could conclude that therapist ratings of adherence were accurate reflections of the content of therapy, which would allow future research to dispense with the need for costly independent ratings.

Supervision structures

The IAPT therapists were supervised by local IAPT leads from the participating centres – both the supervisors and therapists were all British Association of Behavioural and Cognitive Psychotherapy-accredited therapists. The IAPT supervisors from Kingston, Camden and Islington and Bristol were externally supervised by Roz Shafran and those from Greenwich, Coventry and Warwickshire by Michel Dugas. Both external supervisors were ToSCA co-applicants.

Routine supervision of therapy in IAPT takes place at least monthly, but is flexible within this period. However, in this trial, we recommended flexibility so that if any immediate issues needed attention, the therapists could consult their IAPT supervisors. The external ToSCA supervisors (RS and MD) provided additional monthly supervision sessions ('supervision of supervision') by teleconference link to the IAPT supervisors, which was part of the trial process and was in addition to usual clinical practice. The external ToSCA supervisors were also accessible to the local IAPT supervisors by e-mail to answer any additional queries that arose between supervision sessions.

Flexibility in the practice patient stage was used to learn about how clarification and modifications to the CBT intervention might be required. This was done by keeping rigorous notes during supervision to help inform the project, as well as e-mail discussions between the supervisors and the trial team. It was agreed that once the 'practice phase' had finished, there would be no modifications to the protocol allowed.

Findings and recommendations following the practice patient stage

Supervision

Direct supervision of IAPT therapists in the services took place, on average, monthly for between 60 and 90 minutes individually, in pairs or in groups of three or four, depending on the service. The expert 'supervision of supervision' (i.e. supervision of the IAPT supervisors by RS and MD) also took place monthly between July 2015 and January 2016 for 60 minutes. This was done over a dial-in telephone service, with times and dates agreed in advance. Michel Dugas supervised four IAPT supervisors directly and Roz Shafran supervised three. A total of 12 supervision sessions took place, six for each of the supervisors, monthly, with the exception of August 2015. Detailed notes were kept with any queries about protocols minuted and addressed at the next supervision session after consultation with the research team.

Patients treated with cognitive behavioural therapy

Of the team supervised by Roz Shafran, 7 out of the 11 therapists had cases. A total of 16 patients were seen, with a mean of 2.3 patients per therapist; the mean number of sessions was 8.8 (SD 8.5). Of these, three completed ≥ 14 sessions. In 8 out of the 16 cases the GAD checklists (TCC and EoTC) were completed. Reasons for ending therapy in the 16 patients were as follows: two clients completed therapy (one had received 16 sessions and the other was well after 10 sessions), three clients completed prematurely as they did not want to do 'exposure', two were unwilling to allow the recording of sessions, five had not yet completed treatment and four withdrew (one moved, one was too busy to attend and two withdrew without giving a specific reason).

Ease of supervision

Telephone supervision proved to be a useful way for the ToSCA expert supervisors to supervise the IAPT supervisors. The IAPT supervisors were able to represent the views and queries that their local therapists had raised. These are included in the summary of questions on the manual and treatment manual (see *Clarification and modification to treatment protocol as a result of the practice patient stage* below).

Adherence and competence

The TCC and EoTC checklist were completed or partially completed for 8 of the 16 participants seen. The supervisors considered the therapists to be adherent according to the checklist, but noticed that the most common component of the protocol that was omitted was the written exposure.

The supervisors considered the therapists to be competent on the basis of listening to excerpts from their sessions, but none had rated a full session using the CTS-R because of the time required to do so and the fact that not all of the 'practice patients' were being recorded as consent had not been provided for recording.

Clarification and modification to treatment protocol as a result of the practice patient stage

Improving Access to Psychological Therapies protocols

- Patient attendance: the aim in the trial would have been to encourage the therapist to be proactive about following up patients and not to discharge participants unless they had failed to attend at least two sessions without notice.
- Clarification of what constituted a 'step 2 IAPT intervention': the protocol required patients to have received a step 2 IAPT intervention prior to being referred into the study. This was clarified and confirmed early on in the CBT group discussions (see *Figure 1*).
- Spacing of sessions: the Dugas treatment manual (see *Appendix 13*) indicated that patients should attend 14 sessions if possible, to be delivered within 16 weeks. For some, however, they might only complete treatment by 26 weeks. In the practice patient stage, some supervisors reported patients recovering within 10 sessions. It was agreed that if the therapists wanted to discharge patients after fewer than 14 sessions then they should make sure that patients were truly asymptomatic by asking them to complete the Penn State Worry Questionnaire,[60] which is the problem-specific measure of GAD within

IAPT services as well as the GAD-7. If their responses to the questionnaire indicated that the patient was within the normal range and had recovered fully, then they could be discharged with the reasons for this being clearly recorded. It was also agreed that such patients should have received at least two sessions dedicated to relapse prevention.

Study protocol

- Adherence to the manual: the agenda should be set with the patient at the beginning of treatment, consistent with the collaborative approach of CBT, and included in this should be a full clinical assessment of the patient and also a risk assessment, to be conducted during the first 20 minutes of the session. It was agreed that all of the modules in the manual should be covered, but that modules 4 (problem-solving) and 5 (written exposure) could be swapped around. In some clients there was a concern that problem-solving may be used as a way of reducing their tolerance of uncertainty and this could be addressed by delaying the problem-solving module.
- Consent: a prerequisite of participating in the trial is that the patients have agreed to their session being audio-taped.
- Specific therapeutic interventions: it was accepted that some exposure tasks may be more effective than others and the therapists were encouraged to be flexible in their approach. They requested a relapse prevention sheet, which was provided by Michel Dugas (see *Appendix 16*). The therapists were encouraged to undertake exposure to uncertainty experiments in a graded way with their patients, in order to make them more manageable and facilitate engagement.

ToSCA participants (internal pilot proceeding to full trial)

Clear progression criteria were developed and stated to allow progression from the internal pilot to the full trial. One of these criteria was that the therapy could be delivered competently and that the therapists could adhere consistently to the protocol. This was operationalised as stating (1) that the therapists, during the internal pilot, should score a minimum of 36 on the CTS-R within 10% of randomly selected tapes independently rated by the external assessor, and (2) that a minimum of 60% of the components of the protocol had been delivered according to external assessor ratings on the EoTC. The random selection of 10% of audio-tapes taken from the total number of audio-recorded sessions delivered to all patients is commonplace in trials as it ensures that the quality of therapy is representative and the interpretation likely to be generalisable.

Confidentiality

The project aimed to use Data Safe Haven to transfer and store audio-recordings of therapy. This service provides a technical solution for storing, handling and analysing identifiable data. It has been certified to the ISO27001 information security standard and conforms to the NHS Information Governance Toolkit. This is built using a walled garden approach, in which the data are stored, processed and managed within the security of the system, avoiding the complexity of assured end point encryption. A file transfer mechanism enables information to be transferred into the walled garden simply and securely (see *Chapter 3*, *Research governance*).

Chapter 7 Public and patient involvement

Introduction

Public and patient involvement (PPI) for ToSCA was arranged by the McPin Foundation. The McPin Foundation is a mental health research charity with a particular specialism in the involvement of those with experience of mental illness in research.[61]

The McPin Foundation additionally supports service users to carry out research in their own right in collaboration with others. PPI in ToSCA took two forms: first, from Thomas Kabir, one of the study co-applicants; and second, from a group of four service users known as the ToSCA Clinical Advisory Group (CAG).

As the research was the result of a commissioning brief, PPI perhaps had less of an impact at the design stage of the study than would otherwise have been the case. Nevertheless, the study had PPI input in the application for funding and at all subsequent stages of the research.

Methods

Clinical Advisory Group

The CAG was made up of three service users plus the PPI co-applicant. The CAG met roughly three times per year. Ad hoc meetings were held as needed. The responsibility for organising CAG meetings was held by the PPI co-applicant, Thomas Kabir, who is employed by the McPin Foundation.

The CAG members were recruited via an open advertisement. The three people that were subsequently recruited all had personal experience of anxiety. Meetings were chaired by Thomas Kabir. Members of the wider research team were invited to attend meetings, and all meetings were minuted. The minutes of CAG meetings were shared with the research team.

A total of six CAG meetings were held between August 2014 and June 2016. As per the NIHR's *INVOLVE Briefing Notes for Researchers*,[62] CAG members were reimbursed for any out-of-pocket expenses. Members were offered payment for attendance at meetings.

Thomas Kabir was the PPI co-applicant for the study. He provided input into the application for funding to the HTA programme as well as the application for ethical approval. He later:

- sat on the Trial Management Group (TMG)
- attended TSC meetings as an observer
- recruited and organised CAG meetings
- acted as a link between the CAG and the wider study team
- advised on the recruitment materials for the study
- provided ad hoc advice to the study team as needed.

Reflections

A major initial focus of the CAG was on measuring the acceptability from a patient perspective of the two interventions being tested against each other: sertraline and CBT. Developing ideas about how to measure the acceptability of both a psychological therapy and a medication proved to be a particular challenge. In the end, the decision was taken to use the Client Satisfaction Questionnaire (CSQ). The CAG disagreed with this decision, as the CSQ appeared to focus on satisfaction with services rather than treatments per se.

However, the TMG decided on the CSQ because of the perceived need to use one questionnaire to get participant feedback about both interventions in order to be able to use this in the analysis, and no other questionnaires were found that were able to be used to do this.

A related issue arose when dealing with the issue of what outcome measures to use in the study. CAG members felt that the adverse effects of both CBT and sertraline should be measured. This posed a problem, as it proved that there were no measures that were truly applicable to both a medication and a psychological therapy. The CAG suggested using a modified form of the Toronto Side Effects Scale, but the wider study team did not see this as an adequate solution as it was designed with drug-related side effects in mind. The CAG felt that a modified version, taking out some of the terms, could still work, but the wider study team felt it was not possible within the trial timelines to proceed with this. Additionally, there was some debate within the wider study team as to whether or not adverse events that would not be classified as serious in nature should be measured at all, and the TMG noted that the side effects of sertraline have been fully documented in other studies. CAG members held the view that although this was true, the adverse effects experienced by people actually taking part in the study needed to be considered. The idea was that both the adverse and beneficial effects experienced by study participants needed to be weighed against each other to get a true notion of the net worth of the treatments being considered.

As the study progressed, more attention was given over to recruitment issues by CAG members and the PPI co-applicant. CAG members felt that the responses made by the TMG to the recruitment issues that the trial faced were appropriate. Indeed, it was felt that the study team had done all that they could to address the recruitment problems that the trial faced. It was noted from an early stage that recruitment to the study would be challenging. The following extract from the minutes of a CAG meeting held in November 2015 summarised the CAG's position:

> *A possible downside to taking part in the study is that participants will have no choice about whether they take medication or CBT. Outside of the study people can potentially access both treatments. This is clearly a barrier to participation.*

Specific suggestions were made regarding how low-intensity IAPT workers could introduce the study to potential participants. One CAG member wrote a script for IAPT workers to use, which was then shared with other study team members and used in the revised version. More practical issues, such as how best to ask female participants to take a pregnancy test as part of the baseline eligibility interview, were also discussed. The recruitment strategies that were identified by the study team were fully discussed by the CAG.

Summary and recommendations

After the decision had been taken to close the study, a final meeting of the CAG was arranged. This was at the suggestion of both the PPI co-applicant and CAG members.

- Two CAG members felt that communication with them about the study could have been more regular and ongoing. It is recognised that this was as a result of staffing issues within the study team that were beyond anyone's control.
- The CAG patient voice could have been a bit stronger in the study. It was recommended that at least two lay people sit on both the TSC and TMG. There was only one lay member formally on each group.
- It should have been made clearer what could have been measured as part of the study and what could not (i.e. looking at side effects and adverse events of sertraline and CBT).
- CAG members said that they had enjoyed their experiences. One member said that her involvement with the McPin Foundation had been a positive experience. This involvement had helped her become involved in other research studies.

- Everyone felt that the size of the CAG was appropriate. The relatively small size of the CAG enabled the group to discuss quite complex matters in depth. CAG members thought that this might not have always been possible with a larger group.
- All members of the CAG fully recognised the challenges inherent in the study attributable to comparing two distinctly different treatment modalities in which patients are likely to have a preference of one over the other, thus leading to huge challenges in recruitment.

Questions from the Clinical Advisory Group as a result of the study

- The CAG asked if the funder had sufficiently foreseen the potential recruitment problems with the study. The CAG felt that there would be significant numbers of people who would prefer to receive CBT rather than sertraline from the outset. This may have meant that a different study design may have been more beneficial.
- CAG members asked if the commissioning brief for the study was reviewed by people with experience of mental health problems specifically. If so, did these people identify the potential recruitment issues that may arise from the original commissioning brief?

Recommendations for future research

- It seemed that there are relatively few treatment acceptability measures in routine use. It was felt that it would be useful for the NIHR or another funder to fund research into developing a treatment acceptability measure that would be of broad use within a mental health research setting. Within the context of ToSCA, a measure that would work across different treatment modalities (a drug and a psychological therapy) was needed.
- Likewise, there are few (if any) measures that can be used to measure the adverse effects of both a drug and a psychological therapy. Again, it was felt that it would be useful to develop a measure that could be used across different kinds of interventions.

Chapter 8 National Institute for Health Research Health Technology Assessment monitoring meeting

Recruitment was always the main concern of this study. Over the first 2 months of recruitment, six potential participants were identified in the only pilot site at that time open to recruitment. Although this met our anticipated recruitment rate of two participants per pilot site per month, the majority of those identified (4/6) declined to participate in the trial, largely because they were reluctant to be randomised to the medication arm. This trend persisted in the other sites and raised concerns about the study achieving the required numbers over the internal pilot recruitment period. In view of this, the focus of the TSC meeting that was held on 29 September 2015 was to develop an advance plan for an appropriate recruitment strategy. An analysis of the reasons for low recruitment was conducted and discussed at this meeting. However, the main reasons for poor recruitment did not change over time and some of the main reasons for non-participation in the trial by eligible patients, based on the data obtained until the closure of the study, are listed in this chapter.

Review of reasons for poor recruitment

1. Patients' preferences were by far the most important reason for the non-participation of 45 of the 60 potentially eligible patients (see *Table 3*). Of these 45 participants, 30 did not want to take any medication and one for not more than 6 months; four wanted only CBT; one wanted a combination of antidepressants and CBT and one went to their GP to obtain this; one was already on medication (SSRIs); one found it hard to engage with CBT; two did not think that their GAD was their main clinical priority; two did not want to take part in research; one did not give any reason for not taking part; and one travelled extensively and, hence, could not keep regular clinical appointments as would have been expected with participation in the trial.

2. GP factors contributed to the non-participation of four of the remaining potentially eligible patients. In two such instances the GP was reluctant to prescribe medication and take part in the study, and in two cases the GP decided to start sertraline even though they were aware of the trial.

3. IAPT and the PWPs: informal discussions with the PWPs suggested that participants who were potentially eligible to take part but also had concomitant mental health comorbidities (i.e. depression, health anxiety and social phobia) were excluded as possible participants in the study by the PWPs as they perceived that these comorbidities would need to be treated first over and above any GAD. This was compounded by the fact that patients with GAD, by virtue of their illness, were likely to express considerable uncertainty about participation in a trial when approached to participate. This was then also perceived by the PWPs as a reason for excluding them from the study. In addition, potential participants often slipped through the recruitment net in the face of conflicting clinical pressures. Finally, and most importantly, recruitment via a psychological therapy service (i.e. IAPT), as per the HTA programme brief, was biased towards a pool of people who were expecting to receive psychological (CBT) therapies. This meant that presenting such patients with a randomised option of drug or psychological therapy was poorly received, especially considering that they were expecting to receive the latter.

Trial Steering Committee response

These issues were fully explored at the TSC meeting on 29 September 2015, and the chair of the TSC wrote to the HTA programme informing them of the recruitment figures and of the various strategies (please see the following paragraph for further details) that the study team had been working on to address this issue. In response to this letter, the HTA programme arranged a monitoring meeting for 14 January 2016 to discuss both the reasons for the poor recruitment levels and to explore possible alternative methods that could address this issue. At the meeting, a presentation of the various strategies that were adopted by the trial team to enhance recruitment was summarised.

Health Technology Assessment monitoring meeting: strategies adopted to enhance recruitment

1. PPI input to enhance recruitment: we had worked closely with our PPI co-applicant, Thomas Kabir, and the PIs at each clinical site to enhance recruitment by offering eligible participants a balanced view of both drug and psychological treatments for GAD. We refined, with help from the PPI CAG, a user-accessible script that the PWPs would adopt to offer an unbiased account of both treatments while also tackling concerns that people had about antidepressant therapy. This was intended to be discussed with all people with a GAD-7 score of ≥ 10 on completion of step 2 IAPT treatment.
2. Engaging with PWPs at the sites to ensure that they were actively recruiting to the study. This was done by:

    i. the trial team regularly attending PWP site meetings, in which they reminded PWPs about the trial and were available to address any queries
    ii. weekly telephone contacts with sites by ToSCA to field any queries on participant identification and baseline assessments
    iii. 2-monthly teleconferences at which all pilot sites discussed and shared information about effective recruitment strategies.

3. Other methods used to identify eligible patients were:

    i. assisting the identification of potentially eligible people through the IAPTUS database (IAPT's electronic clinical system), as an additional mechanism of identifying potential participants. We initially worked with the lead PWPs in Camden, Islington and Kingston on running the following searches:

        – retrospective searches to identify potentially eligible people missed by the PWPs during their clinical reviews at the end of their step 2 treatment
        – prospective searches to identify potential participants at their entry to the step 2 treatment (i.e. those with high GAD-7 scores not on antidepressants) and alerted the PWPs in advance about their possible eligibility

    ii. IAPTUS prompts to PWPs of potentially eligible people: we were working with the IAPT data managers on generating a computer prompt on the IAPTUS database in order to flag potential participants, as described in the paragraph above. This, however, was not finalised and, hence, not implemented
    iii. approaching people on the waiting list for step 3 (high-intensity therapy): we explored the possibility of getting eligible people to take part in the trial but, as they were on the waiting list for CBT, they were expecting to receive psychological treatments and, hence, this approach did not yield any participants
    iv. opening new pilot recruitment sites: on 13 November 2015 we proposed the recruitment of more clinical sites to boost our study numbers. We had received recent expressions of interest from six sites through our contact with the CRNs and NHS trusts, as well as several over the past year that the study had been advertised on the web. When approached, four sites expressed a definite interest in taking part in the study, but after further discussion only two of these were willing to actively recruit.

These strategies were discussed at the HTA programme monitoring meeting on 14 January 2016. It was made clear that despite all the efforts that had been made by the trial team, recruitment to this study was unlikely to achieve our final target number of 360 participants and we suggested that we alter our recruitment strategy through a protocol change. Prior to the HTA programme monitoring meeting, in discussion with the TSC, we had considered two possible future protocol changes: options A and B.

We requested that one of these two, or both used in succession, be adopted following our meeting with the HTA programme monitoring committee. These two options are detailed below:

1. Option A – this would have involved a drive to identify more people in primary care through a retrospective search of GP databases to identify all adult patients aged ≥ 18 years with Read codes[63] for anxiety/depression and/or GAD-7 scores of ≥ 10. Letters would then be sent to those so identified containing a reply slip, consent form for screening questionnaires, GAD-7 to complete, exclusion criteria assessment checklist and a brief questionnaire asking them to express interest in participation in the study. This approach aimed to maximise the identification of patients with GAD in primary care, and to refer them on to the local IAPT services. The TSC were supportive of this change of protocol as it was consistent with the HTA programme commissioning brief. They were concerned, however, that such a strategy could overwhelm the local IAPT services, which were likely to already be under pressure and may not have been prepared to deal with more referrals. Furthermore, there could be a significant delay while people were receiving step 2 treatment before they became eligible for participation in the trial. This could then lead to high levels of dropout. Nevertheless, the advantage of such an approach was that it was tied in with the changes we had already implemented to enhance recruitment from within IAPT services.

2. Option B – the process of identifying suitable patients in option B would have been similar to that of option A. We would have run a retrospective search of GP databases to identify all adult patients aged ≥ 18 years with Read codes for anxiety/depression and/or GAD-7 scores of ≥ 10. Letters would then be sent to patients containing a reply slip, consent form for screening questionnaires, GAD-7 to complete, checklist of exclusion criteria and a brief questionnaire asking them to express an interest in taking part in the study. Suitable patients would then be assessed for their eligibility to take part in the trial in general practice and then be randomised to either the sertraline medication arm or high-intensity CBT without having to engage with the step 2 treatment as delivered by the PWPs.

Option B would have been essentially a move from the original question proposed in the HTA programme brief as it involved a change in research population. Rather than pointing people towards IAPT teams for step 2 treatment (as in option A), this option would have recruited to the trial without a step 2 intervention. This in itself is an important clinical question, but would have constituted a move from the HTA programme brief as the study would not recruit merely those who have failed to respond to a step 2 intervention as specified in the brief. The TSC initially felt it premature to consider such a departure without (1) testing the effectiveness of the planned current changes to recruitment that would adhere to the HTA programme brief, and (2) seeking the opinion of the funder, the HTA programme, as to whether or not this amendment of the protocol (and thus research question) should be held in reserve if other changes, as described above, had failed to improve recruitment.

Finally, a radical suggestion, bearing in mind that patient preferences are a major hurdle to recruitment, was to design a patient preference trial in the form of a comprehensive cohort preference trial.

The HTA programme monitoring committee was not supportive of option A as this was an approach that would not be adopted within the NHS in the future, even though the proposed protocol change would have adhered to the HTA programme brief. The committee did consider option B to be a viable strategy but, as it represented a significant deviation from the original commissioning brief, they wanted to consult with the HTA programme director in order to arrive at a final decision. At the conclusion of the HTA programme monitoring meeting the trial team was advised to persist with efforts to recruit until further notice was given by the HTA programme regarding whether or not they would allow a deviation from the original commissioning brief. If this was not considered acceptable, we were advised that the trial would be expected to close down, hence bringing the study to an end.

Final decision to close down the trial

On 29 January 2016, following discussions with the HTA programme director, we were informed that a deviation from the original commissioning brief was not considered acceptable and the study should be brought to an end. The principal reasons for this decision were as follows.

1. Fairness, in that any research team that would have submitted a proposal if the commissioning brief had included option B, but chose not to because they felt the commissioning brief as it stood was not feasible or appropriate, would have legitimate cause for complaint if we subsequently proceeded to follow option B.
2. Option B involved a substantial change to the study population and would therefore represent a different research question to that originally commissioned.
3. Option B would appear to deviate from NICE guidance; it was not clear if this would be acceptable to the clinical community.

Following this decision we stopped recruiting to the trial and plans to close the trial down were developed and implemented from 1 March 2016.

Chapter 9 Conclusions and recommendations: implications for practice and research

Main conclusions

Low rates of identification of potential participants

It was unfortunately not possible to recruit sufficient participants to the trial of CBT versus sertraline following the recommended brief. The main barrier appears to have been at the level of identification of potential trial participants by the IAPT PWPs. There are a number of possible reasons for this, which can be summarised as follows:

1. The PWPs potentially having a bias towards psychological therapy as the treatment of choice and finding it difficult to maintain clinical equipoise when talking to the patients about the trial.
2. The PWPs being aware that having GAD meant that these patients found uncertainty very difficult and that the prospect of being randomised to a RCT for their treatment with the associated uncertainty of this was particularly difficult for them to manage; the PWPs felt uncomfortable raising something that might make their patients more anxious.
3. Some PWPs considered that the prevalence of GAD, or having this as the main clinical problem that patients wanted to address, was lower than suggested by the trial team and they were very keen to ensure that the patients they suggested the trial to definitely had GAD, despite the research team explaining that a definitive diagnosis could not be made at the routine PWP level.
4. Several PWPs raised the issue to their clinical supervisors, suggesting that a patient's comorbid clinical or psychosocial problem was more important to address than their GAD. In such cases, the research team encouraged both the PWPs and their supervisors to consider suggesting to patients that they might be assessed for ToSCA if they had significant GAD.
5. Most PWPs had significant clinical workloads and it was difficult for them to also include the time needed to raise the possibility of being assessed for the trial with suitable patients.

Patient factors affecting recruitment once they had been identified

The reasons given by many of those patients who had been identified as not wanting to be recruited into the trial largely mirrored what the PWPs had suggested, in that by far the most significant reason given was that the patient did not want to risk being randomised to the sertraline arm of the trial, and several expressed a clear preference for wanting CBT treatment. Not wanting to be given medication appeared to be the predominant factor, although finding the uncertainty of the randomisation process difficult may also have been a factor. In retrospect, the nature of GAD – worry when there is uncertainty – should have alerted us to the likelihood that discussions about the study and the uncertainty raised by randomisation would prove challenging.

The reasons people gave for declining to participate were predominantly that they were unwilling to try antidepressant medication or that they were clear that they wanted psychological treatment. Although surveys indicate that people commonly report a preference for psychological over pharmacological treatment for common mental health problems, the number of people unwilling to consider antidepressant medication in our study was in excess of what would be expected from these surveys. One possibility is that the context of recruitment within an IAPT service may be significant. The service is focused on psychological treatments (in its name as well as in its treatment provision), and this sets a context for both patients and staff. The IAPT staff approaching patients about the study, however much the need for equipoise was discussed with them, are likely to have had an allegiance to psychological interventions and may have subtly communicated this to potential participants. Even if this did not happen, people opting to

be seen in an IAPT service in the first place are likely to be those interested in psychological treatment and they may well have had less favourable views towards pharmacological treatments.

Another factor that was less of an issue than we had expected and made assumptions for was comorbid major depression – only one patient of the seven who had a baseline assessment was found to be ineligible because of major depression on the MINI questionnaire, which was much lower than we had expected with our 50% estimate, although the number of patients assessed was small. It may have been that by being very selective in the potential patients they identified, the PWPs had excluded those who were clearly significantly depressed. The other patient found to be ineligible at the baseline assessment had found it difficult to be sure whether or not GAD was the main psychological difficulty for which they wanted treatment – after discussion with the TMG we clarified the wording of this screening question to make it less potentially ambiguous.

In advance we had assumed that two-thirds of people meeting criteria for the study in other respects would either be on antidepressant medication or decline to participate. In the event, a little over one-third of potentially eligible people were already on antidepressant medication, and one in five participants approached ended up agreeing to participate in the study.

The fact that two GPs declined to support their patients in their wish to be assessed for the trial was disappointing, but it is difficult to know how we could have avoided this, given the trial design that recruited participants from IAPT who could be registered with any of the GPs linked to that service. The only way to have avoided this would have been to consider only patients whose GPs had agreed in advance to be involved in study, but the response rate to a request from the local research networks for interested GPs to state this was very low, which was not very surprising given that the chances of them having a patient selected to take part in the trial were not high. The only other way to deal with this issue would be to recruit directly from primary care, which is a strategy we considered (please see the following section) and suggested to the HTA programme at the monitoring meeting, but this was turned down by the funders because it would have been a major alteration to the commissioning brief.

Systemic factors affecting participant identification and recruitment

Linked with this is the fact that the advent of the national IAPT programme in England has meant that CBT and related evidence-based psychological treatments are now readily available and accessible as standard treatments. This means that if people have a preference for CBT they can access this relatively easily, in the same way that people have for much longer been able to easily access antidepressant medication via their GP. When access was more difficult, people might have been more prepared to consider a trial, but now if people have a preference they may well exercise this through opting for their preference. Two potential participants demonstrated this by stating a wish to have both CBT and antidepressant medication when the study was discussed with them.

An alternative treatment strategy would have been to recruit from primary care. In primary care, the full range of people with GAD would have been available to recruit, and primary care is where initial discussions naturally take place about treatment options between drug and psychological treatments. People are more likely to be in equipoise between drug and psychological treatments at this point than focused towards psychological treatments, as they are later in an IAPT service and, accordingly, are likely to be more open to accepting randomisation. They would also be less likely to already be on medication. This recruitment option was not available to the study team as the commissioned brief was, following the NICE stepped-care model, specifically to target people who had not improved following a low-intensity psychological intervention. Arguably, the restriction in the total GAD population from the brief as given would have limited the generalisability and utility of the findings even if recruitment had been successful, and recruiting from the wider primary care population would have been more useful and generalisable in the clinical sense. However, it is possible that, even if recruiting in primary care, people would have clear preferences between medication and psychological treatment and, as both are now relatively easy to access in England, they might well exercise that choice and be unwilling to accept randomisation to one or other intervention.

Future research and training recommendations

1. Running a RCT of medication versus psychological therapy involving two interventions that are already readily available to patients through the NHS is likely to have significant recruitment problems because many people will prefer not to be randomised if they are able to choose the treatment they would prefer. This was likely to have been further compounded in this trial by recruiting participants from a psychological therapy service and the difficulty of dealing with the uncertainty of randomisation for people with GAD. However, the unanswered question of whether psychological therapy or medication is more effective for people with GAD remains.

   We would suggest that potential funding bodies consider a call for a randomised trial of medication versus psychological therapy for patients recruited from primary care, as this is where the discussion about treatment choice is likely to occur. Those randomised to the psychological therapy arm could be offered a low-intensity intervention initially and, if they do not improve sufficiently, proceed to high-intensity CBT, with the treatment paths in both arms of the trial clearly documented over the 12-month follow-up. The number of people accepting or declining treatment at each step would provide useful additional information.

   Alternatively, a design that is more likely to reproduce the way in which patients are offered the choice between pharmacological and psychological therapy in practice would be to recruit participants with GAD from primary care to a randomised trial of a pharmacological therapy versus high-intensity CBT without them being referred for a step 2 intervention. This would not be following the NICE stepped-care model, but many patients are likely to be offered the choice between medication and psychological therapy at this stage by their GP and may be more willing to accept being randomised to one of the two interventions, allowing a direct comparison to be made.

2. Given the reluctance of patients to be randomised in this trial (both because of a reluctance to consider randomisation to the medication arm if recruited from the IAPT service, but also because of the uncertainty associated with randomisation, which people with GAD are likely to find particularly difficult), we would suggest that a patient preference design is considered. This could be a comprehensive cohort preference trial design, with patients allowed to choose whether they wish to opt for their preference of treatment or would be happy to be randomised to either intervention, with both cohorts being followed up for the duration of the study and the outcomes in the preference arms compared with the outcomes in randomised arms. However, it is possible that even recruiting via primary care, too few people may agree to be randomised to either intervention.

   The recommendation would, therefore, be that if randomisation is not possible (either with recruitment via IAPT or primary care) then a naturalistic cohort design should be considered, following people up in accordance with their choice of treatment over a 12-month duration.[64,65] It would be important to accurately document all psychological comorbidities that might have an impact on the outcome.

   A further possibility would be to use a Zelen's preference design,[66] with participants being randomised before their informed consent to participate has been obtained, and then being offered the treatment to which they were randomised. This would remove the intolerance of uncertainty as a potential barrier to patient involvement but is likely to also result in significant numbers not wanting to take part, thus reducing external validity. Ethics concerns may also be raised about using this design.

3. GAD appears underdiagnosed in primary care, for a variety of reasons, including imprecise diagnostic classification by GPs, which may have a negative impact on the outcome of people with this disorder. It would be helpful to conduct a study assessing patients diagnosed by their GPs as having depression or other anxiety disorders to see to what extent they may have been misdiagnosed, and conditions such as GAD or other psychological disorders underidentified.

The recommendation would be for a study examining the prevalence of GAD in a primary care population, possibly by reassessing patients diagnosed with a variety of depressive and anxiety disorders with a more detailed gold standard psychiatric instrument. This would also be helpful in establishing the numbers of people with 'primary' GAD, in which their GAD was their predominant concern, and those with comorbid depression or other anxiety disorders that were more of a concern to them.
A further recommendation would be to include semistructured interviews to establish if patients identified as having GAD saw this as a priority for treatment or if depression or other comorbidities were likely to be higher priorities for them.

4. Identification and recruitment of potential participants from our pilot IAPT services proved difficult, despite the enthusiasm of the IAPT leads at the various sites and the fact that we had expressions of interest from a significant number of other IAPT sites around England if the trial continued to the next stage. This was, however, a difficult role for the PWPs to undertake as it was clear that they had a heavy clinical commitment and little experience of research apart from the lead PWPs at each site, who were very energetic in their attempts to improve the recruitment rates.

   We would suggest that training in research methods becomes a more formal part of PWP training if they are to be involved in recruiting for trials on a regular basis.

5. The PPI CAG identified a lack of suitable patient acceptability and adverse event measures that could be applicable to both the medication and psychological therapy arms of randomised trials.
   Funding bodies may wish to commission the design of such an instrument for use in future RCTs.

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Contributions of authors

Marta Buszewicz (Reader in Primary Care) was the CI, involved in the design of the study, writing and submission of the proposal, and had overall responsibility for the co-ordination and delivery of the study. She drafted and edited the final report.

John Cape (Director of Psychological Therapies Programme) was a co-applicant and assisted in the design of the study, as well as playing an active role in liaising with the local sites and training the PWPs during the study. He contributed to drafting the final report, revising it and providing detailed feedback.

Marc Serfaty (Clinical Reader in Psychiatry) was a co-applicant and assisted in the design of the study, and played an active role in refining the processes to be used for rating and validation of the tapes obtained in the CBT intervention arm. He contributed to drafting the final report, revising it and providing detailed feedback.

Roz Shafran (Professor of Translational Psychology) was a co-applicant and assisted in the design of the study, and played a leading role in delivering the research supervision of the CBT supervisors at the pilot sites. She contributed to drafting the final report, revising it and providing detailed feedback.

Thomas Kabir (Public Involvement in Research Lead) was a co-applicant and PPI lead for the study. He assisted in the study design and led the PPI CAG, which reviewed and gave feedback on the study protocol and materials. He contributed to drafting the final report, revising it and providing detailed feedback.

Peter Tyrer (Emeritus Professor of Community Psychiatry) was a co-applicant and assisted in the design of the study and ongoing discussions about amendments to the protocol and attempts to improve participant recruitment throughout the duration of the grant. He gave feedback on the writing of the report.

Caroline S Clarke (Research Associate in Health Economics) was actively involved in updating the various drafts of the study protocol and development of the health economic assessments for the trial. She contributed to revising the final report and providing detailed feedback.

Irwin Nazareth (Professor of Primary Care and Population Health and Joint Director of the PRIMENT CTU) was a co-applicant, assisted in the design of the study and gave ongoing methodological expertise throughout the grant as well as liaising with the staff of the PRIMENT CTU. He covered as CI for Marta Buszewicz for 6 months between October 2015 and March 2016. He contributed to drafting the final report, revising it and providing detailed feedback.

Data sharing statement

As only seven participants were recruited and the trial was closed prematurely with very limited follow-up data obtained, there are no useful data to be shared.

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Appendix 1 Patient information sheet

ToSCA – Trial of Sertraline versus Cognitive Behavioural Therapy for generalized Anxiety disorder

Participant Information Sheet

This information sheet is designed to give you information about a research study comparing whether a medication (Sertraline) or a talking therapy (Cognitive Behavioural Therapy) is the better treatment for people with generalised anxiety disorder.

Invitation to take part

You are being invited to take part in our research study exploring treatment of Generalised Anxiety Disorder (GAD). Before you decide whether to take part it is important for you to understand why the research is being done and what it would involve for you. Please read the following information carefully and discuss it with others, such as your family or friends if you wish. Take your time to decide whether or not you wish to take part. If you are interested in taking part a member of the research teams will go through this information with you and answer any questions. Thank you for reading this.

Why are we doing the study?

GAD is common, causes unpleasant symptoms and affects people's functioning.

It is often chronic and may be accompanied by depression or other anxiety disorders.

Those taking part will have already had low intensity psychological therapy for this condition, but still continue to experience a certain level of symptoms. There are two treatments recommended for GAD when treatment of the kind you have already had has not helped enough. One is a type of medication (Sertraline), the other is a psychological therapy (CBT). Both have been found in many research studies to be effective, but they have never been directly compared. This is a national study comparing these two kinds of treatment to see whether one is more effective. We are very keen to find out more about patients' experiences of treatment and recovery and will be following all participants over the course of a year.

This research will inform future treatment of GAD. We will compare the clinical and cost effectiveness of the two treatments after one year. Findings from the research will help clinicians and service providers to choose the best treatment for people with GAD.

Why have I been chosen to take part?

We are approaching people who are aged 18 years and older who have attended local psychology (IAPT) services for low intensity treatment, but who are still experiencing symptoms likely to be due to GAD. We would like to offer such people further, more intensive, treatment. We are hoping to recruit 360 people nationally to take part.

Do I have to take part?

No, it is up to you whether or not you take part in this study. Whether or not you decide to be involved will not affect the care you receive from your general practice or local psychology service (IAPT). If you would like more information to help you make a decision, please contact the research team using their contact details on the back page.

If you are interested in taking part you will be contacted by a researcher who will arrange a time to go through the study in more detail at a location convenient for you. At this point you will also have the opportunity to raise any questions about the study. You do not have to take part unless you feel completely happy with what you are being asked to do. If you agree to take part, the researcher will ask you to complete a consent form and you will be given a copy. You are free to withdraw at any time without giving a reason. If you do decide to stop taking part we will destroy all identifiable information about you and any recordings.

What will taking part involve?

As you have said you may be interested in the study the research team will contact you shortly by phone, email or letter (whichever suits you best) offering you an appointment to meet with a member of the team. At that appointment you will be given the chance to ask any questions which you may have about the trial and we will make sure that you understand what the research is about.

If you would like to take part in the trial after this discussion we will need to check that you meet a few entry requirements. We have already asked for your permission to contact your GP to ensure there are no medical reasons why you cannot be involved.

We will ask you to sign a consent form before checking your worry and anxiety symptoms to see whether you are suitable to take part. If you are suitable and still want to be involved we will also ask you to complete a few simple questionnaires asking about symptoms of anxiety, depression,

quality of life and your general functioning at this first meeting. This whole interview and assessment should take about one hour.

Women of child bearing potential will be asked to complete a urine pregnancy test at the initial interview, before completing the study assessments, to make sure that they are not pregnant when entering the study. This test will be provided by the researcher.

This is because there is uncertainty about the effect of sertraline on the unborn child and we will therefore not be including any women who are pregnant or planning pregnancy in the near future or breastfeeding, in case they are allocated to the medication group of the trial. For this reason we advise use of contraception for anyone included in the medication arm of the trial in order to avoid pregnancy.

You will be asked to complete the brief questionnaires asking about anxiety, depression and quality of life again at 3 monthly intervals during the year that you are involved in the trial. These will be sent to you by post or email – whichever you prefer. You will be asked to have a further meeting with a member of the research team to review how things have gone 12 months after your first appointment and will be asked to complete the same questionnaires again, as well as the measure of your general functioning. This should take about one hour and can take place at a location that suits you best.

How do you decide which treatment group I am in?

This study is what we call a 'randomised trial'. At the moment we do not know whether the medication Sertraline or CBT will be more helpful in improving people's worry and anxiety in the longer term. We need to compare the two by choosing people to receive one of these two approaches. A computer will be used to pick names at random and put them into one of the two groups. The computer has no information about people, so selection is by chance. You will be told which group you are in by the research team within two working days of the first meeting.

If you are in the group receiving the medication Sertraline

You will be asked to see your GP for this – the research team will have already checked that your general practice is happy to provide this medication for you and will let them know that you are in this trial group. We will ask the GPs prescribing Sertraline and the participants taking this medication to continue doing so for 12 months if possible, in order to investigate its longer-term effectiveness. You will be reviewed regularly by your GP over this time, who will be acting in your best interests at all times. In order to do this, they will ask you to attend for six visits over the 12 months of the study.

Sertraline has been prescribed for many millions of people worldwide for symptoms such as depression and panic and found to be very safe. However, it does not yet have marketing authorisation specifically for treating generalised anxiety, so your GP will need to check that you understand this before prescribing it for you. This does not mean that the medication is unsafe; indeed, many studies have shown it to be safe and effective and it has been selected by the

National Institute for Clinical Excellence (NICE) as the medication most likely to be effective for generalised anxiety. If you are in this group we advise use of contraception while you are taking part in the trial to avoid pregnancy.

If you are in the group receiving Cognitive Behavioural Therapy (CBT)

You will be asked to attend between 14 and 16 weekly sessions of about an hour each with a specially trained therapist. Sessions will be tape recorded to ensure that everyone taking part receives the same quality treatment. These recordings may be used in the supervision sessions for the therapists – this is usual clinical practice with this form of therapy. You will also be asked to complete some standard brief questionnaires at each of the weekly sessions.

How will this affect my usual treatment from my GP?

Taking part in this trial should not affect the treatment you get from your GP in any way. People being prescribed the medication Sertraline by their GP will be regularly reviewed for this and should feel free to discuss any concerns they may have about this treatment or any other medical problems they may be experiencing. Those receiving CBT should feel free to attend their GP as usual.

Are there any disadvantages in taking part?

You will be asked to complete some questionnaires every three months for a year but we will keep these as short and simple as possible, so they should only take 10 to 15 minutes to complete each time. All information will be kept confidential and identifiable only by a special code number, not your name.

Do the treatments have any side-effects?

Some people can get side-effects when starting to take the medication Sertraline, such as feeling giddy, a bit sick or getting a headache, but these are usually mild and short-lived. In a few cases it can make people's anxiety worse to start with, but we are asking people who will be taking the medication to start on a very low dose to minimize the chance of them getting any of these side-effects. Any possible side-effects will be listed on the leaflet accompanying the treatment when prescribed and your GP will be happy to discuss these with you. You will also be given a telephone number to contact the research team if you are concerned.

It is rare to get side-effects from talking or psychological treatments, but some people occasionally find it upsetting talking about their problems with another person, although this usually improves as you get to know them better. If you find it very upsetting you should discuss this with the therapist, and may also wish to mention it to your GP or to the research team via the contact number you will be given.

What are the possible benefits of taking part?

Both treatments offered in this trial are likely to be effective in helping treat your anxiety symptoms, so you should benefit from whichever treatment you are given. The reason we are running this trial is because we are unsure which of the two treatments is best for whom. We will ensure that both treatments are delivered to the highest clinical and quality standards and we will be monitoring your progress throughout.

What are the alternatives for treatment?

If you decide that you are unhappy with the treatment you are offered or think that it isn't effective, you should discuss this with your GP who can suggest a different medication or psychological therapy for you to try. Possible alternative treatments suggested by NICE include several other medications or an addition to the CBT called applied relaxation. (Other psychological/talking therapies have not been recommended by NICE because of a lack of evidence). The two treatments we are using in this trial were given the highest effectiveness ratings for GAD by the NICE panel which is why we are testing them against each other.

What if relevant new information becomes available?

Sometimes we get new information about the treatments being studied. We don't think this is very likely to be the case, but if it happens, we will tell you about it and discuss whether you want to or should continue in the study. If you decide not to carry on, we will make arrangements for your care to continue. If you decide to continue in the study we will ask you to sign an updated consent form. If the study is stopped for any other reason, we will tell you why and arrange your continuing care.

Will my taking part in this study be kept confidential?

Yes. All information collected about you during the study will be kept strictly confidential and in accordance with the Data Protection Act 1998. Any information about you that we collect will have your name and any other identifiable details removed and will be given a special code number. This code number will also be used to identify the questionnaires that you are sent, and the key to the code will be kept in a locked cabinet at the research centre at University College London. Any identifiable information will be stored separately and securely at the research centre at UCL. Only members of the research team and responsible people authorized by the Sponsor, regulatory authorities or from the NHS Trusts involved will have access to this data. All essential documents will be kept in a safe and secure place for a minimum of 5 years after completion of the trial, in case there are any queries raised about the data collected.

Although your GP will be aware that you are taking part in the study, and will know which treatment you are receiving, (s)he will not have access to any other data you provide as part of the research study (e.g. your answers to the questionnaires).

What happens when the research study stops?

We hope that by the time the research study is finished, you will be feeling better, however, if you are not, you will be able to talk to your GP about this and they will be able to arrange for you to have any further treatment necessary.

What will happen to the results of the research study?

None of the people taking part in the study will be identified in reports or publications. The study results will be presented at conferences and published in relevant medical journals. We will send you a brief summary of the results at the end of the study. Copies of any publications can be obtained from the study organisers and sent to any study participants and GPs who wish to have them.

Who is organising and funding the research?

The study is being organised by the Research Department of Primary Care and Population Health, University College London. Funding is from the National Institute for Health Research (NIHR) Health Technology Assessment. Researchers are not paid above their normal salaries if you take part in the study.

Who has reviewed this study?

This study has been reviewed and approved for its scientific methods by independent researchers in the field appointed by the research funder.

In addition, all research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by Brent Research Ethics Committee (REC reference 14/LO/2105).

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions – please see details below.

If you remain unhappy and wish to complain formally, you can do this through your local Clinical Commissioning Group (CCG) Complaints Procedure. Details can be obtained from the relevant CCG. A member of the research team can help you to get these.

Every care will be taken in the course of this study. However, in the unlikely event that you are injured by taking part, compensation may be available. If you suspect that the injury is the result of the Sponsor's (University College London) negligence then you may be able to claim compensation.

After discussing this with a member of the research team, please make the claim in writing to Dr Marta Buszewicz who is the Chief Investigator for the clinical trial and is based at the

Department of Primary Care and Population Health at University College London. The Chief Investigator will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. You should discuss this possibility with a member of the research team (details given at the end of this letter) in the same way as above.

Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff or about any side effects (adverse events) you may have experienced due to your participation in the clinical trial, the normal National Health Service complaints mechanisms are available to you. Please ask your study doctor if you would like more information on this. Details can also be obtained from the Department of Health website: http://www.dh.gov.uk.

What if I have any questions or concerns about the study?

We are providing contact details and telephone numbers and email addresses so you can contact us if you have any questions at any point. We will be happy to ring you back if you wish.

Thank you for taking the time to read this.

Yours sincerely,

Dr Marta Buszewicz (Chief Investigator)
Primary Care & Population Health
University College London
Royal Free Campus
Rowland Hill Street
London NW3 2PF

Email: [redacted]

Tel: [redacted]

Fax number: [redacted]

Dr Anastasia Kalpakidou (Trial Coordinator)
Primary Care & Population Health
University College London
Royal Free Campus
Rowland Hill Street
London NW3 2PF

Email: [redacted]

Tel: [redacted]

Appendix 2 Medication Suitability Review form

Add local header/details

Medication Suitability Review

Date

Dear [GP contact]

Re: TOSCA – a Trial of Sertraline versus CBT for generalised Anxiety
[Patient name and DOB]

We have obtained the above patient's consent to contact you regarding their medical suitability to take part in the ToSCA trial.

ToSCA is a randomised controlled trial comparing the clinical and cost effectiveness of an SSRI treatment (sertraline) versus Cognitive Behavioural Therapy in people with Generalised Anxiety Disorder (GAD) who have not responded to step 1 or step 2 interventions. It is funded by the National Institute of Health Research Health Technology Assessment programme, and coordinated by UCL.

In order for them to take part in the study, we need to know that there is no medical contra-indication to them receiving treatment with sertraline for generalised anxiety disorder if they end up being randomised into that treatment arm. We have been asked to check this at the participant recruitment stage, whichever arm of the trial the patient is randomised into.

Please could you complete the checklist on the next page and email this to [Trial confidential email address] or fax back to [add local fax number]

If you have any questions, please contact us using the details below.

The research team will be seeing this patient within a week of the date of this letter to assess their suitability for the trial and **we would be grateful if you could send your reply to reach us by then. [**Give date here if possible to do this via mail merge.]

Many thanks for your time. The practice will be reimbursed at the agreed rate of £35.

Yours Sincerely

[Site to add local contact details]

Add local header/details

Medication Suitability Review

Patient name:	**YES**	**NO**
Is the patient unable to complete trial questionnaires due to insufficient English or cognitive impairment?		
Does the patient have significant dependence on alcohol or illicit drugs?		
Does the patient have any comorbid psychotic disorder, such as schizophrenia, schizo-affective disorder or bipolar disorder?		
Has the patient received any treatment with antidepressants in the last eight weeks?		
Has the patient received monoamine oxidase inhibitors or pimozide within the past 14 days?		
Does the patient have poorly controlled epilepsy?		
Does the patient have any known allergies to sertraline?		
Is the patient currently participating in another clinical trial involving medication?		
Does the patient have severe hepatic impairment?		
Is the patient currently receiving anti-coagulant medication?		
Does the patient have any form of bleeding disorder?		

In addition, for female patients could you please confirm:

	YES	**NO**
The patient is current pregnant, planning pregnancy or lactating		
The patient is able to conceive		
The patient cannot conceive as post-menopausal		
The patient cannot conceive as they have had a hysterectomy or surgical sterilisation		

Name of GP completing checklist: ……..

Signature of GP completing checklist: …… Date: ……..

Appendix 3 Informed consent form

Centre Number: ☐☐☐

Patient Screening Number for this trial: S C ☐☐☐☐☐☐☐☐

CONSENT FORM

ToSCA – Trial of Sertraline versus Cognitive Behavioural Therapy for generalized Anxiety disorder

Chief Investigator - Dr Marta Buszewicz

Senior Clinical Lecturer, UCL Medical School

Please initial box

1. I confirm that I have read and understand the information sheet dated **X**_____ for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the sponsor of the trial (University College London) and responsible persons authorised by the sponsor, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that my contact details will need to be collected and stored securely by the sponsor of the trial (University College London) to allow questionnaires to be forwarded for completion throughout the duration of the trial. ☐

5. If allocated to the CBT group, I consent to the audio-taping of sessions, to be used for therapist supervision and quality control, within the research study. ☐

6. I agree to my GP being informed of my participation in the study. ☐

7. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 (original) for researcher site file; 1 to be kept in medical notes.

Appendix 4 General practitioner notification of patient not being eligible

UCL

ToSCA
Trial of Sertraline versus CBT for generalised Anxiety

NHS National Institute for Health Research

GP Notification of Patient Not being Eligible

Date

Re: [patient name] [patient DOB]

Dear [GP name]

You have previously been informed about your patient's interest in participating in the ToSCA trial. The ToSCA trial is an NHS NIHR funded randomised controlled trial comparing the effectiveness of CBT and an SSRI medication (Sertraline) for patients with Generalised Anxiety Disorder.

Unfortunately, at the baseline assessment appointment your patient was found not eligible for participating in the trial based on the inclusion/exclusion criteria.

We would like to thank you for your involvement in the trial and we hope to work with you again in the future.

If you have any queries please contact us as below.

Yours sincerely,

Dr Marta Buszewicz (Chief Investigator)
(Trial Coordinator)
Email: [redacted]
Tel: [redacted]

Dr Anastasia Kalpakidou
Email:
Tel: [redacted]

Fax number: [redacted]

Appendix 5 General practitioner notification of randomisation outcome

Notification of ToSCA Participation

Date

Dear [GP contact]

Re: TOSCA – a Trial Of Sertraline versus CBT for generalised Anxiety
[Patient name and DOB]

As you are aware, ToSCA is a multi-centre randomised controlled trial designed to compare the clinical and cost effectiveness of sertraline versus CBT in people with Generalised Anxiety Disorder (GAD) who have not responded to step 1 or 2 interventions for this condition.

This letter is to confirm that this patient has been randomised to receive [insert treatment arm].

- *If randomised to receive Sertraline, please insert the following:*

'Participants randomised to treatment with sertraline are asked to visit their local GP practice for treatment, in accordance with standard recommended clinical care as described in the guidelines provided by the ToSCA trial team.

We have asked [... give name ….] to make an appointment with you within the next two weeks to start treatment with sertraline and have provided guidelines to facilitate this. This includes contact details within working hours to discuss any concerns which you may have. If you have any questions about this please contact us using the details below.'

- *If randomised to receive CBT, please insert the following:*

'An IAPT therapist will contact the patient to arrange for them to start therapy. If you have any questions about this please contact us using the details below.'

Yours Sincerely,

Dr Marta Buszewicz (Chief Investigator)
Email: [redacted]
Tel: [redacted]

Dr Anastasia Kalpakidou (Trial Coordinator)
Email: [redacted]
Tel: [redacted]

Fax number: [redacted]

Appendix 6 General practitioner guidelines for prescribing sertraline

UCL ToSCA Trial of Sertraline versus CBT for generalised Anxiety NHS National Institute for Health Research

Prescribing Guidelines – Sertraline for Generalised Anxiety Disorder in the ToSCA Trial

Treatment of GAD in Primary Care:

The interventions include:

- Step 1 - patient education including identifying substance misuse and co-morbid depressive disorder.
- Step 2 - psychological therapy including individual guided self-help.
- **Step 3 - pharmacological therapy (antidepressant medication) for those patients who have marked functional impairment or whose symptoms have not responded adequately to step 2 interventions.**

GAD: Pharmacological Interventions - Key Points:

There is an evidence base for the effectiveness of the Selective Serotonin Re-uptake Inhibitors (SSRIs). NICE suggests using sertraline first line as it is the most cost effective medication. Please note sertraline does not have marketing authorisation for the treatment of GAD. Verbal informed consent should be obtained from the patient and documented in their notes.

All patients prescribed antidepressants should be informed about potential side effects (including transient increase in anxiety at the start of treatment) and of the risk of discontinuation/withdrawal symptoms if the treatment is stopped abruptly or in some instances if a dose is missed, or occasionally on reducing the dose of the drug.

Trial participants randomised to the sertraline arm of the ToSCA trial will be asked to make an appointment with their GP within 1-2 weeks of being notified about this and the GP practice will be asked to facilitate this appointment.

At the 1st appointment – Time 0 – the GP is asked to:

- confirm they have not been taking any other prescribed antidepressant in the past 8 weeks
- ask about previous treatment response if applicable;
- assess risks of self-harm or deliberate overdose;
- assess possible interactions with concomitant medication;
- confirm that the patient agrees to proceed with the suggested treatment

- The GP needs to check 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 (verbal) informed consent to having it prescribed – prescribing the drug on this basis should be documented in their GP notes
- The recommended starting dose in this trial will be 25mg Sertraline daily for the first week to improve tolerance early in therapy. The GP will need to explain that the patient will need to cut 50mg tablets prescribed in half, as there is currently no 25mg tablet form available.
- If the patient tolerates the 25mg dose for a week they should be advised to increase to a whole tablet or 50mg daily after the first week.
- A brief explanation of the most likely possible side-effects should be given and the appropriate action to be taken in such circumstances.

At the 2nd appointment – within 2 weeks – the GP is asked to:

- 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 would like you to use your normal procedures to review the patient's progress, i.e. clinical judgement and the patient's feedback. Please ask about and note functional change (occupational and social) as well as clinical improvement.
- We want to avoid the use of questionnaires assessing anxiety such as the GAD-7 or Hamilton Anxiety and Depression Scale (HADS) as these are being used as outcome measures in the trial.

At the 3rd and 4th appointments – review at 6 weeks and 3 to 4 months – the GP is asked to:

- Assess the efficacy of the medication and review any potential side-effects.
- Increase the dose of medication dose if required - the anticipation is that the usual treatment dose will be between 50 and 100 mg for most patients, although some might require 150mg.
- We would expect the patient and GP to report some significant improvement by six weeks, with this being well established by 3 months.
- If the patient cannot tolerate sertraline or has not responded, we would recommend that you prescribe an alternative SSRI or SNRI antidepressant in accord with NICE guidelines.
  Any changes in medication should be recorded – this data will be collected by the study team.

At the 5th and 6th appointments – review at 8 months and 12 months:

- If the patient agrees to continue with the sertraline as prescribed and both you and the patient think there has been an adequate therapeutic benefit there should be a further review at around 7 to 8 months and again at 12 months – asking about clinical and functional improvement, concordance with the medication and any side-effects experienced.

General Points:

- The GP must act in their patients' best interests, so if indicated should refer them to secondary care services or psychological treatments. We would prefer trial participants in the SSRI arm not be referred or receiving CBT whilst in the trial, but appreciate this may occasionally happen.
- If the patient is seen in-between these times to discuss their treatment for GAD or issues to do with the medication being received these please document these clearly in their notes.
- Please inform the study team of any serious medical events involving the trial participants whilst they are involved in the study – please see details on the accompanying safety reporting sheet.
- If the patient would like to continue taking sertraline for their GAD after the trial has finished they should discuss this with you and come to a joint decision about their future management.

Appendix 7 Safety reporting information for participants, general practitioners and Improving Access to Psychological Therapies services

Card for participants randomised to CBT:

ToSCA
Trial of Sertraline versus CBT for generalised Anxiety

You are taking part in a CTIMP **trial of** Sertraline Vs Cognitive Behavioural Therapy **in** generalised anxiety

Your treatment = Cognitive Behavioural Therapy

In case of any serious medical problems please contact the Coordinating centre at UCL: [redacted]

If you would like further information please call the Trial Manager on: [redacted] in working hours only.

ToSCA is coordinated by University College London (UCL)

Please carry this card while you are on treatment and show it to any other doctor who may be treating you.

Card for participants randomised to sertraline:

ToSCA
Trial of Sertraline versus CBT for generalised Anxiety

You are taking part in a CTIMP **trial of** Sertraline Vs Cognitive Behavioural Therapy **in** generalised anxiety

Your treatment = Sertraline, dose: 25-150 mg/daily

In case of any serious medical problems please contact the Coordinating centre at UCL: [redacted]

If you would like further information please call the Trial Manager on: [redacted] in working hours only.

ToSCA is coordinated by University College London (UCL)

Please carry this card while you are on treatment and show it to any other doctor who may be treating you.

SAE sheet for GPs

Add local header/details

A Trial of Sertraline versus Cognitive Behavioural Therapy in generalised Anxiety

Safety reporting information for GPs

To help us to ensure the safety of our patients please let us know if any of your patients involved in the TOSCA trial experience any untoward medical events.

We only need to know about the events that meet one of the following criteria:

- Results in death
- Is life-threatening at the time of the event
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in a significant or persistent disability or incapacity
- Consists of a congenital abnormality or birth defect
- Any other important medical condition that carries a real (not hypothetical) risk of one of the outcomes above

Please ask your trial patients whether they have experienced any illnesses at every visit.

If any illness meets one of the above criteria please email the trial team as soon as possible on:

[redacted]

We would need to know as much as possible about the event including, as an absolute minimum:

- Patient name
- Trial number
- Reason for seriousness (one of the above criteria)
- Trial arm i.e. CBT or Sertraline
- Your name and contact telephone number
- What happened to the patient?
- e.g. (patient had a heart attack at home, patient has been diagnosed with diabetes)
- Start and end dates of the event

Please also include the following information if possible:

- Treatment given for the event
- Whether the trial intervention was changed as a result of the event (dosage, frequency)
- If hospitalised, hospitalisation dates
- Where the event happened
- Concomitant medication at the time of the event
- Other medical conditions at the time of the event

If you are unsure about whether or not to notify us of an event please contact a member of the trial team on the above email address or contact the PRIMENT Pharmacovigilance Coordinator on

[redacted]

Thank you for working with us on the ToSCA trial.

SAE sheet for IAPT

UCL

NHS National Institute for Health Research

ToSCA Trial of Sertraline versus CBT for generalised Anxiety

Add local header/details

A Trial of Sertraline versus Cognitive Behavioural Therapy in generalised Anxiety

Safety reporting information for IAPTs

To help us to ensure the safety of our patients please let us know if any of your patients involved in the TOSCA trial experience any untoward medical events.

We only need to know about the events that meet one of the following criteria:

- Results in death
- Is life-threatening at the time of the event
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in a significant or persistent disability or incapacity
- Consists of a congenital abnormality or birth defect
- Any other important medical condition that carries a real (not hypothetical) risk of one of the outcomes above

Please ask your trial patients whether they have experienced any illnesses at every visit.

If any illness meets one of the above criteria please call the trial team as soon as possible on:

[redacted]

Thank you for working with us on the ToSCA trial.

Appendix 8 Generic site-specific information justification

ToSCA - Trial of Sertraline versus CBT for generalised Anxiety

The trial design comes from an NIHR HTA commissioned call, which state that participants should have generalised anxiety disorder (GAD) and have not responded to step 1 or step 2 psychological interventions for this as recommended by NICE. This follows from a research recommendation in the NICE GAD guidelines aiming to establish whether CBT or medication is more effective for these step 3 patients – no direct comparison has ever been made.

Because of the design required to answer this question we will be recruiting participants via the IAPT (Increasing Access to Psychological Therapies) services which is where the step 2 psychological interventions are delivered. They will be identified by the low intensity IAPT workers reviewing their case and if they are interested in being considered for the trial their details will be passed across to a member of the research team who will make contact, send them a full patient information sheet (PIS) and then consent and assess them for eligibility if they wish to take this forward. The IAPT centres will be full sites if they are involved in the research team processes listed above – this will be via their Clinical Study Officers (CSOs) or other appropriately trained research active staff.

We will only know at the point of participant consent and randomisation which general practice they are linked with. In order to mirror usual practice we have designed the medication arm with the patient's GP prescribing the medication if they are randomised to this arm of the trial. We will be working with up to 180 general practices nationally for this arm, as each participant may come from a different general practice. We will not be asking the GPs to follow any formal protocol, rather we will be advising them to follow usual clinical guidelines in the way they prescribe Sertraline for GAD. They will be free to alter their patient's treatment as they consider necessary and clinically indicated. This design has been approved by the MHRA who have approved the trial as a level A CTIMP or lowest risk.

A single site-specific information (SSI) form has been created to address the only general practice aspect of the study which differs from usual clinical practice, which is data collection for research purposes. Once a potential participant has expressed an interest in the trial, at the same time as arranging a baseline assessment to check eligibility, the research team member will contact the patient's GP (with the patient's consent) to ask them to complete the medical suitability form. This is a simple form asking for yes/no answers with regard to whether there are any known contra-indications to the patient being prescribed Sertraline if they are randomised to that arm of the trial. We consider that this must be established for safety reasons and before randomisation to avoid any bias between the two trial groups.

The other component of patient data we will need to collect from the patients' general practices is the health service outcome data for all trial participants. This will cover items such as the number of GP and practice nurse appointments attended, referrals to secondary care psychology, psychiatry and general medical services and prescriptions of psychotropic medication. This will either be collected by a member of the practice staff or a member of the research team with a valid local research passport. All data will be pseudonymised before leaving the practice and identifiable only by a numerical ID. NHS assurance is being requested at former PCT level as there is no requirement to gain individual assurance from each general practice.

Appendix 9 Training workshop for high-intensity cognitive behavioural therapy therapists

The workshop covered background information, diagnostic criteria of GAD, the clinical presentation of GAD, the cognitive behavioural model, and treatment and conclusions. Some specific questions about the trial were raised during the training and were addressed by the CI and co-applicants.

The training consisted of providing information about the design of the trial, followed by taking trainees through the six typical phases of the treatment protocol:

1. psychoeducation and worry awareness training
2. re-evaluation of the usefulness of worry
3. uncertainty recognition and behavioural exposure
4. problem-solving training
5. written exposure
6. relapse prevention.

The training was delivered as a workshop, with scenarios in which attendees were encouraged to get into groups and practise using role play. It was based on the manual provided by Michel Dugas, and each therapist and supervisor was given a copy for use in the trial (see *Appendix 13*).

Appendix 10 Training for psychological well-being practitioners

The training sessions followed a common presentation format covering:

1. rationale and design of the study
2. PWPs' role in the study
3. GAD identification and diagnosis.

Presenting the rationale and design of the study included the context of the study in terms of the evidence base for CBT and SSRIs as treatments for GAD, and the current lack of any head-to-head study determining which may be the more effective treatment. The NICE guideline stepped-care model for GAD and the associated clinical recommendations were presented in order to explain the choice needing to be made by the patient and their clinician between CBT and SSRIs as treatment options at step 3 in the NICE stepped-care pathway (see *Figure 1*). This provided the background for the study design as involving the recruitment of patients who had not improved in a step 2 low-intensity psychological intervention, which is why PWPs were critical to the identification and recruitment of study participants as they are responsible for delivering low-intensity psychological interventions within the IAPT services.

Discussion of the criteria for identifying participants who might be suitable for the study and how best to approach potential participants was the central part of the training.

Four key study criteria were set out for PWPs to use in considering patients they were treating:

1. that they were coming to the end of a low-intensity PWP treatment (having had at least three treatment sessions)
2. that they still had a GAD-7 score of ≥ 10
3. that they might have GAD either as the sole diagnosis or comorbid with other diagnoses
4. that they were not currently, and had not for the past 8 weeks been, on antidepressant medication (whether or not a patient was currently on a psychotropic medication was a data item that PWPs are asked to routinely record at each appointment as part of national IAPT data requirements).

Questions from the PWPs and discussion around these criteria during the training sessions mostly focused on:

- whether or not patients in all types of PWP treatment should be considered (the answer to this was yes, with the exception of signposting interventions)
- whether or not to approach patients who, it was decided early in their low-intensity treatment, were unlikely to progress (the answer was yes, as long as they had three treatment sessions)
- how sure they needed to be that someone had GAD (the PWPs were told that they did not need to make a definitive diagnosis of GAD and were encouraged to be inclusive and refer to the study if they thought there was a possibility the patient might have GAD).

Following the discussion around participant identification criteria, PWPs were given a script of what they might say to a potential participant about the study (*Box 3*). The script was developed with suggestions from a PPI member of the CAG (see *Chapter 7*).

The PWPs were encouraged to ask questions about this script during the training session and the advantages for patients in taking part in research studies, as well as any potential barriers, were explored.

BOX 3 Suggested text for PWPs talking to potential participants about the study

> *There are two treatments recommended for the kind of worry and anxiety you have, when initial treatment of the kind we have been working on together has not helped sufficiently. One is a type of medication, the other is a psychological therapy and, although both have been found in many research studies to be effective they have never been directly compared to see whether one is more effective than the other.*
>
> *Our service is participating in a national study comparing these two kinds of treatment and we are therefore suggesting that suitable people take part, as there is evidence that people involved in medical research often do better, whichever treatment group they are included in.*
>
> *You might be interested to join this study and, if so, I can pass your details to a member of the research team who would be happy to discuss it in more detail with you, or if you would prefer I can give you a leaflet that explains more about the study and gives the details of how to contact the research team yourself.*
>
> *Might you be interested? However, if you are certain that you would definitely like to have one of these treatments rather than the other it might be better that you didn't volunteer for this study, as it will involve people being randomised or selected by chance to be in one treatment group or the other.*

Linked to this, the importance in randomised studies of discussing the two study arms from a position of equipoise was emphasised. It was stressed that equipoise was the current state of evidence for this important clinical question, but that they should be aware that they individually might well have a greater investment in psychological than pharmaceutical treatments given that they were working as PWPs and that this could potentially influence how they discussed the study with patients, including subconsciously. How to guard against this was rehearsed.

The final element of the training was about the identification of GAD. GAD DSM-IV diagnostic criteria were outlined and the differential diagnosis from other anxiety disorders and depression. Specific questions PWPs might ask the patients when screening for GAD were described.

The length of the training sessions varied from 1 to 2.5 hours depending on the site.

The longer training sessions included more about the background to the study and longer sessions on GAD diagnosis and identification (these sites had expressed an interest in using the study and the training sessions as an opportunity to train their PWPs in the identification of GAD). One training session was held for each pilot site, with the exception of Camden and Islington with Kingston, which had three training sessions, one for each Borough service.

All the training sessions were delivered by one of the co-investigators (JC), who had established and been the clinical lead of an IAPT service, so had a good understanding of the services and the role of PWPs within this.

Appendix 11 Research staff training

Participants were given an introduction to the trial and its aims and objectives. The research staff had all had some training in obtaining informed consent but were given an update and taken through the ToSCA consent form as well as the structure and format of the eligibility check and baseline assessment procedures. The procedures required asking female participants of child-bearing potential about the need to have a pregnancy test as part of the eligibility criteria, and how to do this sensitively and interpret the results was discussed and practised within the group.

The research staff then took part in interactive training in how to complete the relevant sections of the MINI.[43] This involved working in pairs, taking it in turns to role play scripted vignettes of potential patients with pure GAD (eligible) and also GAD with comorbid major depression and alcohol dependence (not eligible). The group then discussed its results and any queries regarding results that differed from the agreed consensus.

Training was also given in completing the HAM-A.[12] This involved one of the clinical co-applicants (JC or MB) role playing a patient with GAD, and each trainee rating their symptoms and presentation for the 14 items of the questionnaire. At the end the results were once more discussed within the group to ensure a consensus of within two points on each item.

The central research team produced a full training/recruitment manual for participating sites, with all the relevant questionnaires and outcome measures as appendices for reference.

This was distributed in draft version to participants at the training sessions and the full electronic version sent to the pilot sites when they were open to recruitment (manual available on request).

Appendix 12 ToSCA general practitioner flyer

NHS National Institute for Health Research

ToSCA
Trial of Sertraline versus CBT for generalised Anxiety

Add local header/details

Study Objective

ToSCA is an NHS NIHR funded randomised controlled trial comparing the effectiveness of CBT and an SSRI medication (Sertraline) for patients with Generalised Anxiety Disorder (GAD).
Both CBT and SSRI medication are effective treatments for GAD and recommended in the NICE GAD guideline, but there has never been a study directly comparing their effectiveness. The current guidelines say that if a patient with GAD has not responded to step 1 (GP based) or step 2 (Low Intensity IAPT) interventions then the choice of treatment between a pharmacological or psychological treatment at step 3 should be based mainly on patient preference.

This trial aims to provide a clear answer to the clinical query of which is likely to be the most effective: 14-16 sessions of high intensity CBT delivered by IAPT **or** the SSRI sertraline at a recommended dose

How are we recruiting patients for this study?

Potential participants will be identified by Low Intensity (LI) IAPT workers from those people they see who score > 10 on the GAD-7, are likely to suffer from GAD and have not responded to step1 or 2 interventions for this. With the patient's permission they will pass their details across to the research team who will send them full details of the study and see them to assess and consent them for the trial.

What would we like local general practices to do?

- We would like the practice to agree in principle to prescribe sertraline for any of your patients randomised to that arm of the trial
- If any of your patients are identified by the LI IAPT service as potentially eligible we would like you to check their medical suitability to take part and fax / email this information to the research team For any of your patients randomised to the sertraline arm we would like you to prescribe this according to the trial protocol for this. This would involve 6 patient visits over a 12 month period, but only mean seeing and treating people according to recommended normal clinical practice.
- We would like to health services data at the end of the study, including the number of GP appointments attended, secondary care referrals and psychotropic medication prescribed. We are happy to do the relevant search, but can also fund someone at the practice to help with this.

Benefits of taking part in the study

For the patients – best practice treatment for GAD whichever trial arm they are in
For the practice – reimbursement of £ 35 per patient checked for medical suitability to take part, + £140 per patient treated in the medication arm (likely to only be one or two patients per practice)
+ £20 per participant for helping to collect health services data

Recruitment period

Spring 2015 to December 2017

To find out more about the study please contact

Dr Marta Buszewicz (Chief Investigator)
[redacted]

Dr Anastasia Kalpakidou (Trial Coordinator)
[redacted]

Appendix 13 Cognitive behavioural treatment manual for generalised anxiety disorder

Trial of Sertraline versus Cognitive behaviour therapy for generalised Anxiety (ToSCA)

Cognitive Behavioural Treatment Manual for Generalised Anxiety Disorder

Michel J. Dugas, Ph.D.

Université du Québec en Outaouais

Centre de Recherche du CSSS de Gatineau

January 2015

Correspondence: Michel J. Dugas, Professor of Psychology, Université du Québec en Outaouais, 283 Alexandre-Taché, P. O. Box 1250, Station Hull, Gatineau, Québec, Canada, J8X 3X7

Typical Sequence of Treatment

Module	Typical number of sessions
1. Psycho-education and Worry Awareness Training	1-2
2. Re-evaluation of the Usefulness of Worry	1-2
3. Uncertainty Recognition and Behavioural Exposure*	3-4
4. Problem-Solving Training	3-4
5. Written Exposure	3-4
6. Relapse Prevention	1-2
Length of treatment	14-16 sessions

* Exposure to uncertainty exercises should continue until the end of therapy.

Module 1
Psycho-education and Worry Awareness Training

Principles of Cognitive Behaviour Therapy

The present manual is designed to supplement cognitive behaviour therapy for generalised anxiety disorder (GAD). Because the therapy is based on an educational model, the client will need to remember and apply a number of important principles. The manual is divided into different modules, each one adding to the client's ability to deal with worry and anxiety. In order to help the client prepare for therapy, there are a number of basic principles about cognitive behaviour therapy that he should be aware of. The following paragraphs present and discuss these principles.

At the beginning of therapy, the therapist should present and discuss the principles of cognitive behaviour therapy (CBT) with the client. This is very important because the client may not know what to expect from this type of therapy. By discussing the principles of CBT with the client, the therapist will be in a position to help the client have realistic expectations with regards to therapy and to correct any misconceptions about the therapy process and what it involves. The therapist should address these principles right from the first therapy session.

Cognitive behaviour therapy (CBT) is based on a model of the emotional disorders that emphasizes the relationship between our thoughts, behaviours, and emotions. In other words, when we change the way we think, this will have an effect on the way we behave and feel. Likewise, when we change the way we behave, this will have an effect on the way we think and feel. And as you might expect, when we change the way we feel, this will have an effect on the way we think and behave. CBT relies on the bi-directional relationship between your thoughts, behaviours and feelings to help you feel less worried and anxious, and attain a better quality of life. The first principle of CBT that you need to know about is that CBT will provide you with a new way of understanding your problem. When you have been living with your problem for some time, you may have developed ways of understanding it and dealing with it that end up maintaining the problem or even making it worse. CBT will help you to see your problem in a new light and this will point to other ways of understanding your problem and dealing with it on a daily basis.

CBT will also help you develop new skills to address your problem. We know that understanding a problem is one thing, but actually changing it is quite another. To change your problem, I will help you to develop new skills and use these skills to change the thoughts, behaviours and emotions that are contributing to your worry and anxiety. For example, you will learn to generate new ideas about your problem and tests these ideas in your day-to-day activities. In this way, you will be able to make up your own mind about what is causing your worry and anxiety. Because CBT relies on the active collaboration between the client and therapist, you will not be put in a position where you feel out of control. You will be actively involved in the therapy process and your input will be extremely valuable right from the start of therapy. After all, you are the expert

when it comes to your problem and I am the expert when it comes to understanding your problem in a new light. By working together, it stands to reason that we will be able to find better ways of helping you feel better. As a matter of fact, the more therapy progresses, the more you will take the lead in finding ways to deal with your worry and anxiety. This is because CBT aims to help you become your own therapist. It is very important that you not feel overly dependent on therapy because therapy cannot go on forever. When therapy ends, if you have not become your own therapist, you will be at greater risk for relapse. However, if you have become your own therapist, you will be in a better position to face the obstacles that might come your way. In fact, we know that having confidence in your ability to face adversity is one of the best predictors of maintaining therapeutic gains. By having an active role throughout therapy, you will be able to develop the confidence you will need once our sessions are over.

Another way that CBT will help you become your own therapist is by being brief and time limited. As a general rule, CBT typically lasts 10 to 20 sessions. We know that when therapy last for many months (and sometimes many years), it is easier for the client to begin to feel dependent on the therapist. Once you have gained a new understanding of your problem, developed new skills, and used these skills to successfully deal with the problem, it will be important for you to try out these skills on your own. By dealing with your problem without having the security of our weekly sessions, you will be able to further develop your confidence in your ability to be your own therapist. CBT is also structured and directive; that is, it relies on guided discovery. By setting up "experiments" together, you will be able to test out new ideas and see if they are more accurate reflections of your reality. In a sense, in CBT the therapist is the guide and the client makes the discoveries. I will not try to convince you that I am right; however, I will help you to come up with new ideas and ways of testing these ideas.

Another important principle is that CBT is primarily based on the here and now. Although there is no doubt that our developmental history has contributed to who we are today, CBT distinguishes between what may have contributed to the development of a problem and what is maintaining that problem today. In most cases, the factors that maintain a problem are not the same ones that originally contributed to the development of the same problem. To use a well-worn example, if I fall off a horse, I may develop a fear of horses. However, my fear will be maintained if I begin to avoid horses and refuse to "get back in the saddle." In this example, the fall caused my fear but my avoidance of horses is maintaining my fear. I cannot change the fact that I fell off the horse; however, I can change my avoidance behaviour. CBT primarily addresses the factors that are maintaining the problem because these are the factors that are directly accessible in the here and now. Finally, in CBT, between-session exercises are a central element of therapy. There is no doubt that a weekly 50 minute session is not sufficient to change ingrained patterns of thinking, behaving and feeling. In CBT, the client is encouraged to apply new skills on a daily basis. Even if the client finds the therapy session extremely interesting, if therapy does not lead to change in his life, then the client and therapist are wasting their time. In

summary, CBT aims at helping the client attain change in the here and now by using new skills on a daily basis.

Therapy Session Format

Following the presentation and discussion of the principles of CBT, the therapist should present the format for the therapy sessions. Specifically, the sessions will be divided into four parts. The first part of each session will be devoted to reviewing the between-session exercise for the past week. During this time, the client and therapist discuss the new information obtained while doing the exercise, as well as the client's conclusions. In the second part of each session, the therapist presents new information to the client. For example, information about the principles of CBT was provided in the current session. In the third part of each session, the client and therapist discuss how the new information relates to the client's worry and anxiety, and how it can translate into concrete changes in the client's life. In the final part of the session, the therapist and client agree on a between-session exercise for the following week. The exercise should integrate the new information and should gently "nudge" the client to reach a new level of improvement. At the end of each session, the therapist provides the forms for the exercise if forms are required.

The Symptoms of GAD

Before trying to change a symptom, the client should have a very clear idea of how the symptom is experienced. This is especially important in GAD given that its main feature, excessive and uncontrollable worry, is a covert event that cannot be observed by the therapist. In this part of therapy, the therapist presents the "symptoms" of GAD. These symptoms include "What if…?" questions, worry, anxiety, demoralization, and fatigue. As therapy progresses, the therapist will present the factors that contribute to the symptoms of GAD.

Situational Variables

There is often a "situation" (in the broad sense) that triggers the chain of symptoms. This situation can be any event, or even any memory of an event, that elicits a "What if...?" question. For example, having a difficult personal encounter, becoming aware of a physical sensation, reading a newspaper article, or watching a television newscast may all trigger the worry cycle.

"What if…?" Questions

"What if…?" questions are thoughts that begin with "What if…" or the equivalent (for example, "Wouldn't it be terrible if…"). These questions are not the sole source of the problem, but they provide an opening for excessive worries to begin.

Worries

Worries are thoughts set in motion by "what if…?" questions. They usually involve a chain of several ideas, such as "What if my work contract doesn't get

renewed, I don't know how I will pay all my debts, I won't have a penny to spare, I won't be able to keep my head above water, I might not be able to keep my car, etc." In order to avoid any misunderstandings, and to ensure a thorough understanding of worry, it is important that the client and therapist agree on a definition of the concept. A simple and useful definition that we use is the following: Worry is a cognitive phenomenon (a thought process), which is concerned with future events where there is uncertainty about the outcome, the future being thought about is a negative one, and this is accompanied by feelings of anxiety.

Some worries are triggered by external, observable situations (for example, an argument with a friend). Others are triggered by internal events (for example, a physical sensation that might be the first sign of a serious illness). Many worries can even trigger other worries (this is referred to as the *chaining* of worries). For different individuals at different times, worrisome thoughts can last from a few minutes to several hours. Worries can encompass a wide variety of subjects; however, each person will have recurring worry themes. Worries always concern something negative that may happen in the future. Although a worry may be related to some past event, it actually has most to do with the future implications of the event ("after that argument, our relationship will go downhill"). Worry is seldom experienced without discomfort; it is usually accompanied by feelings of anxiety. Often, greater levels of anxiety accompany more severe worries. As a matter of fact, your level of anxiety may be a good way to identify your most important worries.

Worries can be separated into two major types: (1) those that concern current problems (the problem already exists); and (2) those that concern potential problems (the problem doesn't exist yet, and in many cases, never will). This distinction will serve as a guide in choosing the intervention. It stands to reason that different ways of coping may apply to different types of worries (hint: you can't solve a problem that doesn't exist yet!). Some worries are more difficult to classify than others. Sometimes you may feel that there's not enough information to decide with any certainty whether the worry is about a current problem or if it is about a potential problem, but this is normal. The important thing is to choose the category that seems to fit the best, and continue with the appropriate strategy (it's an important part of therapy to make decisions in spite of uncertainty).

Anxiety

Generally speaking, anxiety is the emotional discomfort that accompanies worry. In other words, chronic worry coincides with anxiety (so that if worries decrease, so will anxiety). Anxiety may take the form of physical responses (for example, muscle tension, fatigue, and insomnia) or psychological responses (for example, irritability, nervousness, or difficulty concentrating). It is important to keep in mind that worry is a type of thought whereas anxiety is a type of emotion. We know that thought influences emotion and emotion influences thought. So it follows that if you are able to better control your worrisome thoughts, you will also feel less anxious. Furthermore, if you feel less anxious, it

will be easier for you to control your worry (and so on). Later on in therapy, we will see how your behaviours fit into this equation.

Demoralization and Fatigue

States of demoralization and fatigue often occur when worry and anxiety become chronic and excessive. Such states are often the long-term consequences of the following sequence: Occurrence of problem situation → "What if…?" questions → worry → anxiety. The loss of energy that this process entails can provoke states of demoralization and fatigue. These states often make it more difficult to be actively engaged in therapy. For this reason, therapy will progress at a gradual pace and as you begin to feel less demoralized and fatigued, you will be able to take bigger steps in therapy.

Between-Session Exercise

The client's exercise involves taking note of everyday worries. This requires that the client take note of his worries three times a day, at predetermined times, and indicate the type of each worry on the Worry Diary form.

Worry Diary

Name: Date: Therapist:

Date and time (3 times/day) Date	Time	Worry	Anxiety 0 to 10 (None to Extreme)	Worry type (current or potential problem)

Module 2
Re-evaluation of the Usefulness of Worry

In Module 2, the therapist helps the client to examine his beliefs about the usefulness of worrying. Interestingly, research shows that beliefs about the usefulness of worrying are quite variable in GAD clients. Although most GAD clients believe that worrying is highly useful (and that it might be dangerous to worry less), a minority of GAD clients do not hold many of these beliefs. Thus the therapist should not assume that all GAD clients believe that worrying is highly useful. Nonetheless, given that beliefs about the usefulness of worrying may interfere with all treatment phases (e.g., a client who believes that worrying less would be dangerous may be inclined to avoid fully engaging in therapy), it is crucial that the therapist assess (and in most cases, address) these beliefs early on in therapy.

It is now well established that most people with GAD believe that worrying is more useful than do people who are moderate worriers. Although worry is often a negative experience that is associated with feelings such as anxiety and stress, you may think that worrying is useful for some reason or another. For example, you might believe that the act of worrying actually helps you find solutions, or protects you or nurtures you in some way. Identifying the beliefs you hold about the usefulness of your worries is necessary in order to be able to verify the foundation of these beliefs, and to put them to the test. The adjustment of these beliefs will help you to reduce your tendency to worry. I am not saying that worrying is never useful; however, I am saying that people with GAD tend to overestimate the actual usefulness of worrying. So the question you must ask yourself is the following: "Is worry really that useful; if I worried less, would that really lead to bad things happening?"

Types of Beliefs

There are many types of beliefs that a person can have about the usefulness of worrying. Research has identified at least five types of beliefs about the usefulness of worrying. People with GAD tend to endorse each one of these beliefs to a greater extent than do moderate worriers.

1. The belief that worrying helps one to find solutions to their problems. This has to do with any belief about the usefulness of worrying in helping to solve problems, helping to find better solutions, increasing vigilance, increasing preparedness, contributing to a more well thought out or efficient reaction, or even helping to prevent or avoid problems. Although low levels of worry may at times be helpful in thinking of solutions to problems, high levels of worry actually interfere with the problem-solving process. This is because worry makes us see all the ways our solutions might fail. So worry, in many cases, actually makes solving problems more difficult.

2. The belief that worrying motivates one to get things done. You may believe that if you worried less, you would not get things done. Many people with GAD think that worrying about something is a good way to motivate them to do something about it. In this case, worrying about something appears to get

confused with caring about something. If a person worries less, this does not mean that they will become complacent; it simply means that they will be less stressed about the situation while getting things done. In fact, being highly worried about something often leads to inactivity because of the negative emotional reactions that are associated with worry.

3. The belief that worrying protects one from negative emotions. These are beliefs that worrying will shield you from difficult emotional reactions; that being worried "ahead" of some event occurring will protect you against disappointment, sadness, and guilt. Many people with GAD believe that worrying is like "putting money in the bank" for later. They believe that if the said event takes place, they will have already invested in their negative reaction in advance, thereby allowing them to be less affected by the event. Some of our GAD clients have told us the following: "If something happens to someone I love and I haven't worried about it in advance, I will feel very guilty." This way of thinking puts the person in a position where they must worry constantly, just in case.

4. The belief that worrying, in and of itself, can prevent negative outcomes. The fourth type of belief states that worrying, on its own, can have an effect on the outcome of events; that our worries are directly responsible for the non-occurrence of negative events. This type of belief is sometimes referred to as "thought-action fusion." An example of this type of belief might be "I've always worried about my child being involved in a serious car accident. It has never happened, so my worrying must be working. I have to keep it up."

5. The belief that worrying represents a positive personality trait. "I'm the worrier in my family. If I worried less, my family would be disappointed in me. They would think that I just don't care about them anymore. By worrying, I show them that I care, that I am a good person." This example illustrates the fifth belief about the usefulness of worrying. In this case, worrying is confused with caring. Do people who worry less really care less about the ones they love? It might be a good idea to ask others about this… would your loved ones look down on you if you worried less?

To help the client re-evaluate his or her beliefs about the usefulness of worry, the therapist can use the lawyer/prosecutor role-play. In this role-play, the therapist first asks the client to identify a specific worry (e.g., "worrying about my children shows that I care about them"). The client then takes on the role of a lawyer who must convince the members of a jury that the specific worry is useful. Once the client has finished arguing for the usefulness of the worry, he then takes on the role of a prosecutor who must convince the members of the jury that the worry is in fact not useful. This role-play allows the client to consider "both sides of the coin" in a non-threatening context. Consistent with the principles of motivational interviewing, the therapist can use Socratic questioning to help the client query the actual usefulness of worrying when playing the role of the prosecutor. In this case, examples of questions include: "Is there anything else you do that shows you are a caring parent? Do you know any caring parents who don't worry excessively?" The ultimate goal of the role-play is to help the client increase his motivation for change by questioning the actual usefulness of worrying.

Between-Session Exercises

There are two exercises that accompany this module. The first exercise asks the client to review the different types of beliefs about the usefulness of worrying, write down personal examples for each belief, and identify other beliefs that he has about the usefulness of worrying. The second exercise asks the client to list the advantages and disadvantages of worrying in general. This last exercise can be seen as a complement to the lawyer-prosecutor role-play, which addresses the usefulness of specific worries. These exercises are not meant to completely change the client's beliefs about the usefulness and advantages of worrying, but simply to get the client thinking about the possibility that worrying is not as useful and advantageous as previously believed.

Beliefs About Worry

Name: Date: Therapist:

Below are a number of beliefs that people can have about worry. They have been grouped into different categories. First, indicate by checking off "YES" or "NO" whether you have experienced each type of belief about worry; if "YES", write down a personal example for each.

1. Beliefs about worry as something that can help you to resolve problems. This means all beliefs that convey the idea that worrying helps to fix problems, that worrying can help you find better solutions, become more aware of problems, be better prepared to face them, react better when problems occur, and foresee potential problems and avoid them.

   YES: _____ NO: _____

   Personal example: _____

2. Beliefs that worry is a good way to motivate yourself. This means all beliefs that convey the idea that worrying will motivate you to do things you would otherwise avoid. These beliefs can relate to responsibilities at work, household tasks, social activities, or leisure activities.

   YES: _____ NO: _____

   Personal example: _____

3. Beliefs about worry as protection from negative emotions. This means all beliefs that convey the idea that by worrying, you can protect yourself from negative emotions, that the fact of worrying about something beforehand can protect you from deception, disappointment, or guilt.

   YES: _____ NO: _____

   Personal example: _____

4. Beliefs that the act of worrying can have an effect on events. This means all beliefs that convey the idea that the act of worrying itself can have an effect on events, that worries have power over the occurrence or non-occurrence of positive or negative events.

   YES: _____ NO: _____

   Personal example: _____

5. Beliefs about worry as a positive personality trait. This means all beliefs that convey the idea that a person who worries is considerate, prudent, and cares about the well-being of other people. These beliefs also imply that worrying about someone is proof of love or caring.

   YES: _____ NO: _____

   Personal example: _____

Can you think of any other examples of beliefs about worry, that don't fit into the preceding categories?

YES: _____ NO: _____

If YES, please describe: _____

Advantages and Disadvantages of Worry

Name: Date: Therapist:

Please list all of the advantages and disadvantages of worrying that you can think of. Remember to include how your worry affects you emotionally, how it affects your personal and professional life, and how it affects those around you.

ADVANTAGES OF WORRYING	DISADVANTAGES OF WORRYING

Module 3
Uncertainty Recognition and Behavioural Exposure

Intolerance of Uncertainty

In Module 3, the therapist introduces the notion of intolerance of uncertainty to the client, helps the client see how intolerance of uncertainty leads to worry, and guides the client in beginning to change some behaviours that result from intolerance of uncertainty. Because increasing tolerance for uncertainty is the cornerstone of treatment, the therapist should strive to integrate tolerance for uncertainty into every therapy module.

Research has clearly shown that the way in which a person deals with uncertainty predicts how much they will worry. In other words, a person who is intolerant of uncertainty will worry more than a person who is not. What is intolerance of uncertainty? It is a type of "psychological allergy" to uncertainty. In medical terms, a person with an allergy to a given substance would have a strong reaction to a very small quantity of that substance while most others would not react in the same way. Intolerance of uncertainty is similar to an allergy, in that a person who is intolerant of uncertainty will have a strong reaction (excessive worry and anxiety) to a very small quantity of uncertainty. Thus if something is very unlikely (like one's plane crashing), someone who is intolerant of uncertainty may worry about it nonetheless because there is still a chance (albeit, very small) that it might happen.

How does intolerance of uncertainty lead to excessive and uncontrollable worry? First, intolerance of uncertainty leads to a greater quantity of "What if…?" questions for any given situation. This is because a person who is intolerant of uncertainty tends to focus on all the bad things that might happen. Even if most of these bad things have almost no chance of happening, that person will worry about them because there is no ironclad guarantee that they will not happen. Unfortunately, life holds few guarantees… In addition to this, the "What if…?" questions generated by one's intolerance of uncertainty are not fleeting or temporary. Actually, such intolerance leads to stronger reactions than those of people who are more tolerant. This occurs, in part, because of an increase in the tendency to make mistakes when estimating the probability and consequences of various possible outcomes. Therefore, all these possible outcomes and their consequences are imagined. Such events set into motion a series of thoughts that eventually lead to excessive and uncontrollable worrying.

A person who is intolerant of uncertainty will try to avoid, get around or eliminate uncertainty in a variety of ways. This can be extremely difficult. Why? Because uncertainty is an unavoidable part of everyday life. Uncertainty, or at least some degree of uncertainty, is impossible to avoid. For example, we can never be certain that we will be in good health in the coming year even if we are presently healthy. Also, we cannot know for certain if we will always have a job or if our relationships will always be congruous (this is partially due to the fact that these things depend on several factors that are beyond our control). Once

we recognize that intolerance of uncertainty plays a role in worrying, we can ask: "I know that I am intolerant to uncertainty, but how can I change?"

First of all, we should identify the "target." In other words, what do we want to change? Is it preferable to aim at increasing our level of certainty or increasing our level of tolerance? Of course, the answer to this question is increasing our level of tolerance. However, there is an important difference between acknowledging our intolerance of uncertainty and changing it. It is a big step to understand our intolerance, but it is difficult to change our ideas or attitudes simply by thinking about them. At this point, it is important to add action to ideas. We often hear about people who have the intention of changing certain attitudes; however, the attitude doesn't change because the person doesn't take any action that would bring about the change. It follows that personal conduct is a special means to modify one's attitudes and ways of thinking. Given examples like wanting to stop chewing nails or wanting to lose weight, it is clear that just acknowledging a problem is not sufficient; we must also change our behaviour. This is also true of attitudes, which are not readily observable. For example, we can be conscious of why we are nervous when speaking in public (because we are afraid of being scrutinized by others), but this is insufficient to diminish our anxiety. However, if a person repeatedly practices speaking in public, they will eventually come to believe others will not harshly criticize them if their speech is not perfect. Research has shown that the best way to change deeply rooted thoughts is through action. This is referred to as *experiential learning.*

In order to increase your tolerance of uncertainty, you must follow a course of action, as you would to change any other attitude. At first, you must act as though you are tolerant. Although this may not feel "right" because you are not yet tolerant of uncertainty, it is the best way to start. Specifically, you must ask yourself the following question: "If I were tolerant of uncertainty, what would I do in this situation?" You may often have a good idea of what you should do, but you may not think you can do it. This is normal, especially if you have had to struggle with uncertainty for a long time. The following suggestions will help you to face uncertainty.

Suggestions When Facing Uncertainty

As you probably know, when we try out a specific behaviour for the first time, we often feel uncomfortable. This is not a sign that the behaviour is inappropriate or that we should not do it again. Actually, it is quite normal to feel discomfort during initial attempts at new behaviours. The problem is that we might "use" this discomfort as a reason to not undertake challenging new behaviours. If we expect to feel perfectly comfortable when we engage in new and challenging behaviours, we will not engage in them because a certain amount of discomfort or uneasiness is quite normal. Think of the first time you rode a bicycle or drove an automobile, chances are that you felt some discomfort because of the novelty of the situation.

In order to follow a realistic course of action, it is important to pre-determine an ascending degree of difficulty for the action; that is to say, we should start with

something small and attainable. Then, we will continue to choose increasingly difficult actions. You might also think of this as setting *proximal goals* for yourself. Research has shown that when our goal is far away, it seems unattainable and our motivation to change may disappear. By setting small goals that are clearly attainable (proximal goals), you will be able experience success and build on this success to attain larger goals.

The final principle that will help you to face uncertainty is one that few people know about. Despite what we might think, motivation does not usually precede action – it follows it. In fact, once we have started to act differently, and we have accomplished the initial behaviour change (even if it is a very small change), the satisfaction of having accomplished the behaviour increases our motivation to continue. The realization that we were capable of carrying out this new behaviour and attaining our goal increases our self-confidence. The new abilities that we have begun to develop stimulate us to continue. That is to say, the more you get the more you want.

What type of actions will allow you to increase your tolerance of uncertainty? There is an unlimited supply of actions that can bring about a greater tolerance toward uncertainty. For things of minor importance, you might try the following actions: calling a friend just to say hello when you're not sure of their reaction; ordering a meal in a restaurant that you have never tried before; going to see or renting a movie that you know nothing about; or buying a present for someone without asking any questions to the person the present is for.

Between-Session Exercises

There are two exercises that will help the client become aware of his way of dealing with uncertainty and actually begin to develop a greater tolerance for uncertainty. The first exercise involves completing the Manifestations of Intolerance of Uncertainty form. By filling out this form, the client will begin to get a better idea of how intolerance of uncertainty affects his way of dealing with day-to-day activities. The second exercise involves facing uncertainty and taking note of observations on the Uncertainty and Behaviour form. The goal of this task is not so much the action itself, but more the development of new ways of dealing with uncertainty.

Manifestations of Intolerance of Uncertainty

Name: Date: Therapist:

Below are a number of manifestations of intolerance of uncertainty that have been reported by individuals with GAD. These examples illustrate how a person may act when faced with different kinds of situations. First, indicate by checking off "YES" or "NO" whether each of these manifestations of intolerance of uncertainty applies to you; if "YES", write down a personal example for each.

1. Avoiding doing certain things. YES: _____ NO: _____

   For example:

   Avoid investing in a friendship or romantic relationship.

   Avoid committing to therapy, because the outcome is uncertain.

   Personal example: _____

2. Finding imaginary obstacles not to do certain things. YES: _____ NO: _____

   For example:

   Finding excuses not to take steps to move out of the family home.

   Not doing exercise that you know is good for you, by telling yourself beforehand that you might not be able to stand the discomfort of exercising.

   Personal example: _____

3. Procrastinating (putting off what you could do right away). YES: _____ NO: _____

   For example:

   Putting off a phone call because you're not certain how the person will react.

   Not doing anything in the end, because you are not certain that you made the best choice (e.g., choice of film or restaurant).

   Personal example: _____

4. Wanting to do everything yourself, and not delegating tasks to anyone else.

   YES: _____ NO: _____

   For example:

   Doing all the housework yourself because otherwise you can't be certain that it will be done right.

   Personal example: _____

5. Only partially committing to a relationship, a job, or a project. YES: _____ NO: _____

   Personal example: _____

6. Getting a great deal of information before doing something. YES: _____ NO: _____

   For example:

   Reading a lot of documentation.

   Shopping for a very long time before choosing a present for someone close to you.

   Personal example: _____

7. Questioning a decision you have already made, because you're no longer certain that it is the best decision. YES: _____ NO: _____

   What type of decision? _____

8. Looking for reassurance (asking others to reassure you). YES: _____ NO: _____

   Who do you ask? _____

   In what kind of situation? _____

9. Reassuring yourself with exaggerated optimism, or by always trying to explain everything rationally. YES: _____ NO: _____

   Personal example: _____

10. Double-checking things by re-doing them, because you're no longer sure you did them in the first place (i.e., things that you usually do automatically). YES: _____ NO: _____

    What kind of things? _____

11. Over-protecting others, doing things for them. YES: _____ NO: _____

    Who, for example? _____

    Concerning what type of thing? _____

12. Are there any other ways in which you are intolerant of uncertainty that don't fit into the 11 categories above? YES: _____ NO: _____

    What are these behaviours? _____

Exposure to Uncertainty

Name: Date: Therapist:

What is my chosen behaviour?

What, if any, discomfort did I feel while doing it?

What were my thoughts while doing it?

Now that I have done it, what do I think?

Module 4
Problem-Solving Training

Module 4 is devoted to helping the client improve his or her problem-solving ability. Problem-solving training addresses the client's worries about current problems. Although research indicates that GAD clients do not necessarily have deficits in all problem-solving skills, all components of the problem-solving process should be addressed in order to maximize treatment benefits. In this way, the client and therapist may address the interactions between the different problem-solving components. The therapist should keep in mind that the primary goal of problem-solving training is not necessarily to solve the client's immediate problem; rather, the main goal is to help the client develop sound attitudes and skills that will be helpful in dealing with many of life's small and large problems. Stated differently, the procedures presented in this module are not "full-proof" – they are however "state-of-the-art."

Worries about current problems are addressed by applying sound problem-solving principles to the problem situation. Research shows that people with GAD sometimes have difficulty solving everyday problems for a number of reasons. The most important of these reasons is referred to as negative problem orientation. Problem orientation essentially refers to how a person sees and reacts to problem situations. A person with a negative problem orientation tends to recognize problems when it is "too late", to see problems as an abnormal part of life, and to see problems as threats to be avoided rather than challenges to be met. A person with a negative problem orientation will have great difficulty applying their problem-solving skills and actually solving their everyday problems. And if problems remain unsolved, the person will continue to worry about them…

But having a positive problem orientation is only the first step in the problem-solving process. In order to become an expert at problem solving, one needs to master all steps of the problem-solving process. The five steps to sound problem solving are the following:

1. Problem orientation
2. Problem definition and goal formulation
3. Generation of alternative solutions ("brainstorming")
4. Decision making
5. Solution implementation and verification

Improving Problem Orientation

We will begin by examining ways to improve your problem orientation and then move on to the other problem-solving steps. As mentioned above, problem orientation involves how we see and react to problems. Research shows that people with GAD often see their problems and react to them differently than do people who are moderate worriers. This negative problem orientation can manifest itself in many ways. We will examine three common manifestations of a

negative problem orientation: (a) the failure to recognize a problem before it is too late; (b) believing that it is not normal to have a problem; and (c) seeing the problem as a threat rather than a challenge.

Recognizing a Problem Before It Is Too Late

When a person does not want to have to deal with problems, they sometimes avoid seeing the problems that come up in day-to-day life. Often, problems begin small, and if nothing is done to solve them, they begin to grow and become more complex. Unfortunately, a person who does not want to deal with problems often ends up having much more serious problems to deal with. Imagine that you had a misunderstanding with someone at work and decide to not think about it. That person may begin to hold a grudge and believe that you just don't care. They may then begin to tell your co-workers about the problem and the problem may begin to grow and become more complex as others are brought into the situation. By the time you decide to deal with the problem, it may have become a minor crisis at work with many people involved. So by trying to avoid dealing with the problem, you have gotten yourself into a position where you have to deal with something much more difficult and complex. This example clearly shows the importance of dealing with problems as soon as they arise and "nipping them in the bud." We suggest two ways of helping you recognize problems before it is too late.

The first strategy is to use your emotions as cues that there may be a problem. When you are feeling anxious, stressed, or demoralized, you may want to ask yourself "Is there a problem I am not seeing that is leading to these emotions?" Our emotions, when we are attentive to them, can be very useful for recognizing problems. This strategy has two advantages. First, as previously stated, it will allow you to recognize your problems more quickly. Second, it will help you to see your negative emotions in a more positive light. Negative emotions are not all bad as they serve a utilitarian purpose: they provide you with important information and can help you to recognize your problems. This might help you to feel less stressed about being anxious or less demoralized about being discouraged.

The second strategy to help you recognize your problems is to make up a Recurrent Problems Checklist. We all have problems that tend to re-occur. Every time the problem "goes away", we may believe that it will not return. But it invariably does at some later time. Examples of recurrent problems include problems with a work colleague, problems with your spouse, problems with your children, and end-of-month financial problems. Every time these problems re-occur, we tend to react to them as if they were occurring for the first time; it may take us a long time to recognize them and we may be surprised and disappointed. By preparing a personal Recurrent Problem Checklist, you will be able to recognize these recurrent problems more quickly. Furthermore, you might find that you will be less surprised and disappointed when the problems occur because you "knew they would."

Seeing Problems as a Normal Part of Life

If a person believes that it is not normal to have problems, they may try very hard to avoid all problems. But this is simply not possible. Having to deal with problems (sometimes small, sometimes large) is a normal and unavoidable part of life. Try to find someone who has no problems and you will come to the same conclusion. If a person believes that it is not normal to have problems, they will spend more time feeling annoyed by the problem than trying to solve it. It is much more useful to put that energy into solving the problem and not worrying about it anymore. In order to see problems as a normal part of life, you can try the following suggestions.

If a person attributes a problem to personal incompetence or deficiencies, they will have difficulty seeing the problem as a normal part of life. If you believe that you have problems because you are flawed in some way ("I just don't have it when it comes to getting along with people"), you will tend to see your problems as being abnormal. Remember that everyone has problems no matter how intelligent, sociable, good looking, or skilful they may be. It may seem that some people do not have problems, but this is probably because they deal with them quickly and efficiently. So by not attributing your problems to "who you are", you will be able to see your problems as a normal part of life and you will be able to deal with them more efficiently.

Sometimes people see the problem as a normal part of life but believe that all problems can be solved quickly and completely. In other words, they believe that it is not normal that some problems take time and effort to solve. This could not be further from the truth. Some problems are very complex and require much time and effort to solve. In fact, many problems cannot be solved right away. For example, if you have a problem with your boss and he is away on holidays, you will have to wait to address the problem. Likewise, if you have health problems that can be improved by changing your lifestyle, it will take time for the change in lifestyle to have positive effects on your health. In today's "quick fix" world, it is easy to forget that some things, including solving problems, take time. So by remembering that it is quite normal that solving some problems takes time and effort, you will be in a better position to solve your problems efficiently.

Seeing Problems as Challenges Rather Than Threats

There is quite a difference between a threat and a challenge (or opportunity). Most notably, we usually try to avoid threats whereas we often try to take on challenges. So seeing a problem as a threat rather than a challenge will have quite an impact on how we deal with it. It is well established that people with GAD tend to see problems as threats to be avoided rather than challenges to be met. You may be thinking: "Yes, but my problems ARE threatening." And of course, you are correct. However, if you could see your problems a little less like threats and a little more like challenges, this would make quite a difference. In order to help change your perception of your problems, you can consider the perception of threat and challenge as two extremes on a continuum:

Threat ←----------→Challenge

Seeing a problem completely as a threat or completely as a challenge are both extreme ways to view a problem. There are a multitude of points between the two extremes. The idea is not to regard the problem as a 100 % challenge, nor to see the problem as a 100 % threat. You may have the tendency to view many problems as 100 % threats. Some problems are more difficult than others; therefore, it can seem more difficult to see them as challenges to be taken advantage of (at least partially). The idea is to ask yourself: "What is the challenge for me in this situation?" Here are three examples of how perceptions of threat can be moved towards perceptions of challenge:

Example 1: A job interview

Initial reaction: "I hate interviews. Why do I have to go through this agony? I never do well in these types of situations. I will make a fool of myself just like the last time. I just wish it was over."

Then try: "I'm really nervous before going to an interview. What is the opportunity for me in this situation? Well, maybe I need to learn to show what I am capable of doing. Interviews are not easy, but it would be great if I could learn to sell myself. That is a skill that I will need many times in my life. I guess I could try to look at this as an opportunity to get experience interviewing and to get better each time."

Example 2: A Conflict with your Boss

Initial reaction: "What a jerk. I can't believe he doesn't understand that I have too many responsibilities. Why does he keep giving me more? I can't take this. I'm probably going to burnout and have to take two months off. This is terrible."

Then try: "I really have too much work. I'm feeling stressed out and I don't think I can continue like this much longer. It's really difficult for me to tell my boss that I have too much work. What is the challenge for me in this situation? I guess I need to develop the ability to speak frankly with my superiors or else they will never know how I feel. In a way, I could see this problem as an opportunity to develop those skills. No matter what happens, it is important that I sit down and speak with my boss."

Example 3: The illness of a loved one

Initial reaction: "My father is suffering from a serious illness that requires expensive treatment. Why does this have to happen to our family? It's awful to have to spend so much money on this medication; one day he won't be able to afford it any longer. This is so unfair."

Then try: "What is the challenge for me in this situation? It is certainly difficult to see how illness can be a challenge. I guess I could see this situation as an opportunity to show my father just how much I really care. I could help out as much as possible and show him that I am with him all the way. Although I am certainly distressed, I see this as an opportunity to be strong for someone I love."

In summary, the way we perceive and react to our problems has a considerable impact on our ability to deal with them. By improving your problem orientation, you will be in a much better position to use your problem-solving skills for your problems, big and small.

Between-Session Exercises

Many exercises can be carried out to help the client improve his problem orientation. One specific exercise is suggested here but the client and therapist may wish to develop other exercises. A relatively easy and effective way to improve one's problem orientation is to prepare a list of recurrent problems. The client can complete the Recurrent Problems Checklist and keep the checklist with him at all times. In this way, the client will be able to recognize problems more quickly and react to them with less anger and disappointment.

Recurrent Problems Checklist

Name: Date: Therapist:

The purpose of this list is to help you identify certain problems that recur most often in your life, and also to help you recognize these problems more quickly and easily. These problems can arise in different aspects of your life (e.g., relationships with loved ones, friends or strangers; at work or at school; during your leisure time; while you carry out your day-to-day tasks).

List of problems

Improving Problem-Solving Skills

As mentioned at the outset of this module, there are four other components to the problem-solving process. These four components, which are referred to as the problem-solving skills, are the following: problem definition and goal formulation, generation of alternative solutions ("brainstorming"), decision making, and solution implementation and verification. The skills will be presented in turn along with suggestions for improving the application of each one.

Problem Definition and Goal Formulation

Before trying to solve a problem, one must properly define it. Although this may seem obvious, our clinical experience has taught us that many people try to find solutions to problems that are vague and confusing. We have also observed that many of our clients do not separate their problems and end up trying to solve many problems at once! Needless to say that when a person tries to solve many problems at once, the solution turns out to be disappointing. When one becomes aware of a problem, it is necessary to define it in a clear and concise way in order to generate effective solutions. A problem that is not well defined will lead to ineffective solutions, or even worse, to behaviours that will make the problem worse. For example, if you are experiencing problems at work and you define the problem in a very vague way ("My boss is an insensitive person who takes advantage of me"), you will have difficulty generating solutions to the problem ("How can I make my boss more sensitive?"). If, on the contrary, you define the problem clearly and specifically ("My boss gives me too many files to work on"), you will increase the chances of generating effective solutions ("I will set up a meeting to discuss this issue and ask for a 5 % reduction in the number of files I handle"). In order to adequately define a problem, you can ask yourself the following questions:

1. "Who is involved in the problem?"
2. "What is happening that disturbs me?"
3. "When does the problem occur?"

Generally speaking, the same principles apply to goal formulation; our problem-solving goals should be clear and concise. If your problem-solving goals are vague and confusing, how will you know if you have reached your goals? Only clear and concise goals will allow you know if you have successfully solved your problem. A second set of principles also applies to goal formulation: your goals should be realistic and attainable. The formulation of unrealistic or unattainable goals almost always leads to disappointment and loss of confidence in our problem-solving ability. Therefore, if your problem-solving goals are clear and concise as well as realistic and attainable, you will increase your chances of becoming an expert in the art of problem solving.

Generation of Alternative Solutions

The generation of alternative solutions is often referred to as the brainstorming stage of the problem-solving process. The object of this problem-solving step is

to generate as many alternative solutions as possible so as to increase your chances that the best solution will have been generated. Although this notion may appear very simple at first glance, we know that very few people actually generate multiple solutions before making their decision. Most people generate only one solution and then apply this solution without considering other possibilities. Why is this so? Because there are many obstacles to generating multiple solutions. The first obstacle is habit. Although our habits can sometimes speed up the problem-solving process, they can also keep us from finding the best solution. For example, if you apply old reflexes to new problems, your solution may not be adaptive and effective. The second obstacle is convention. By doing things in a conventional way, you may have the impression of doing the "right thing", even when this is not the case. In order to generate as many solutions as possible, the following principles have proven to be extremely useful.

1. Quantity principle: This principle states that the more solutions you generate, the more quality solutions you will have to choose from.

2. Deferment-of-judgment principle: According to this principle, you will generate a greater number of quality solutions if you suspend judgment of the solution ideas until a later stage of the problem-solving process. As a matter of fact, it is very important to generate all kinds of solutions, even those that seem a little "crazy." You may not end up applying these crazy solutions, but they may make you think of other solutions that aren't so far-fetched…

3. Variety principle: This principle states that the greater the variety of solutions generated, the more good quality ideas will be made available. This principle underscores the importance of being creative when generating solutions so that a wide range of solutions will be available.

If these principles do not allow you to generate many alternative solutions (after having made a considerable effort), you may want to try again with the help of someone else. The goal of this problem-solving step is to generate many (at least 10) alternative solutions that include a wide variety of ideas. Do not forget to include a few "far-fetched" solutions just for good measure! One final suggestion: you may want to combine different solutions to generate new ones that are more complex. In our clinical experience, we have seen many clients combine two far-fetched solutions to make one excellent solution.

Decision Making

Once you have generated many potential solutions, you will be in a position to make a decision as to the solution of choice. The goal of this problem-solving step is to select the best solution among the available options. This is quite different from looking for the perfect solution. The search for a perfect solution is an important obstacle to decision making because the perfect solution probably does not exist! Generally speaking, you

must assess the arguments for and against each alternative solution. At this stage, it is a good idea to proceed by using the "process of elimination." First of all, you should eliminate all solutions that are clearly inappropriate and inferior (they have already served their purpose). Next, you can ask yourself the following questions for each remaining solution.

1. "What are the chances that this solution will work?"
2. "What are the short-term and long-term implications of this solution?"
3. "What are the implications of this solution for me and for others?"

By asking yourself these questions, you will increase your chances of selecting a solution that brings about a desirable outcome for you and for others in both the short and long term.

Solution Implementation and Verification

The final step of the problem-solving process involves the application of the chosen solution and the assessment of its impact. In other words, did this solution allow you to attain the goals you formulated at the start of the process? The application of a solution is influenced by our behavioural skills; therefore, it may be necessary for you to practice certain skills before applying the solution in the actual problem situation. For example, before asking a person to change a specific behaviour, it may be useful to practice with someone close to you. In this way, you will receive valuable feedback about your way of asking a potentially delicate question. Once you have implemented your solution, you can assess its impact on the problem situation and on your mood. Because the problem-solving process is closely related to your distress (problems are problems because they are distressing), an effective solution should help you to feel better. If the solution does not allow you to reach your problem-solving goals, then you can return to the decision-making stage and select another solution. However, if you have reached your goals, then the problem-solving process is over. You can reward yourself for a job well done by doing something that you really enjoy.

Between-Session Exercises

Problem-solving skills can be improved by solving a current problem and taking notes on each step using the Resolution of a Problem form. The form will help the client to pay attention to each step of the problem-solving process and improve their chances of successfully solving the target problem.

Resolution of a Problem

Name: Date: Therapist:

Description of the problem:

Possible solutions:

Chosen solution:

Application of the solution, evaluation of the results:

Observations, comments:

Module 5
Written Exposure

Written exposure is used to address worries about potential problems. These worries often concern major life events that are very threatening and that relate to the client's main fears. Examples of these worries include worrying about becoming seriously ill, worrying about a loved one being involved in a serious accident, worrying about going bankrupt, and worrying about being alone and isolated. Although exposure is very effective for the treatment of worries about potential problems, it can also be intimidating for clients. Therefore, before engaging in written exposure, it is very important that clients understand and accept the theory behind exposure. The following paragraphs present the key constructs underlying written exposure for worry, and provide an example of how these constructs can be presented to the client.

We will now begin to address your worries about potential problems. Have you ever wondered why some people worry constantly about terrible things that could happen someday, like losing someone they love, whereas others do not necessarily spend a lot of time dwelling on these things? The answer to this question may surprise you: it has to do with how a person *reacts* to their worries. However, before discussing how our reactions can lead to more or less worry, there are certain principles of fear that you should know about. In order to better understand these principles, we will start with an example of a specific and concrete fear: the fear of flying. Once you understand how the fear of flying can be extinguished, we will return to your worries and see if we can apply the same principles.

Imagine three different people with the fear of flying. The first person (Robert) has decided to *avoid* taking the plane altogether. Why? Because he knows that *avoidance* is the quickest way to decrease his anxiety. It is not surprising, therefore, that we are "programmed" to avoid the things that scare us. In other words, our natural reaction to something we fear is simply to avoid it. By never going near an airplane, Robert does not have to deal with the uncomfortable feelings of anxiety or any scary thoughts about the plane crashing. The down side of course is that he will never be able to get over his fear of flying; in fact, his fear will most likely increase with time. Research has clearly shown that although avoidance leads to an immediate decrease in anxiety ("I feel much better since I decided to take the train instead"), it also leads to an increase in fear in the longer term ("I couldn't do it last time, so I certainly won't be able to do it this time"). This is referred to as the *avoidance trap*. Although avoidance works very well in the short term and is our natural reaction to fear, it almost always creates a serious problem in the long term as our fear begins to increase and generalise to other situations. Another problem with avoidance is that it often robs us of our quality of life. Someone who constantly avoids new situations can end up leading a life with fewer and fewer opportunities to learn new things. In summary, although Robert does not have to deal with anxiety in the short term, his fear will increase and his quality of life will likely decrease with time.

Imagine that the second person (Patrick) has read a book on the negative long-term effects of avoidance. Knowing that avoidance will not be helpful, he decides to try taking a plane for a brief trip. Two hours before departure, however, Patrick begins to feel more and more anxious and to experience repetitive thoughts about the plane crashing. He then decides to buy a novel at the airport bookstand and begins reading at a furious pace to get his mind off the flight. Much to his relief, the strategy is helpful: he is now feeling less anxious. This is referred to as *neutralisation* (or *safety behaviour)*. Specifically, Patrick has decided to read a novel in order to decrease his anxiety and negative thoughts. The key point here is that Patrick did not buy a book because he felt like reading; rather, he bought the book to decrease his anxiety. *Neutralisation* can involve anything one does (or thinks) to manage feelings of anxiety when facing a fearful situation. One hour before departure, at boarding time, Patrick must put away his book. Once he does so, the anxiety immediately returns and continues to increase while on the plane. Patrick then decides to close his eyes and imagine that he is at home, in his living room. Although it is difficult to keep this image in his mind, his anxiety is now slightly less elevated. Again, Patrick is using neutralisation to keep his anxiety under control while facing his fear. Unfortunately, although he has been very courageous in facing his fear (i.e., getting on the plane), he does not notice any benefits after the flight. In other words, his fear of flying seems unaffected. Why? Because he used neutralising strategies to manage his anxiety before and during the trip. We know now that neutralisation interferes with the extinction of fear when a person is confronted with a fearful situation. In a nutshell, when we neutralise, we cannot learn that the feared situation is perhaps not as dangerous as it seems. In addition, we do not learn whether we can cope with being in the situation without using all sorts of "tricks" to manage our anxiety. In summary, although Patrick has worked very hard to face his fear, he is not reaping any benefits from the experience because his neutralising behaviour is getting in the way of new learning about the situation and about his anxiety.

Finally, let's imagine a third person (Elaine); she has learned that avoidance and neutralisation are not effective strategies to decrease her fear of flying. Like Patrick, she decides to book a flight for a brief trip. Two hours before departure, Elaine notices that she is feeling more anxious and is beginning to have thoughts about the plane crashing. Elaine then decides to do something she has never done before in response to her anxiety: *nothing*. She simply remains seated at the departure gate without trying to control her anxiety or her thoughts. Although her anxiety level remains high, it does not seem to be constantly getting worse. Moreover, after a while, her anxiety actually seems to come down a bit (and the thoughts about the plane crashing are less frequent). Once on the plane, Elaine begins to feel more anxious. Rather than trying to imagine herself elsewhere, she simply decides to "ride out the storm" and experience the anxiety and negative thoughts during the flight. After a while, however, her anxiety begins to gradually decrease, and she is able to endure the last part of the flight with considerably less anxiety. What Elaine has done is referred to as *functional exposure*. Simply put, *functional exposure* refers to facing one's fear without neutralising. As you may have guessed by now, exposure is the best way to decrease fear. Why? Because exposure allows us to learn new things about a feared situation and

about our anxiety. By avoiding or neutralising, we are not able to learn that we are in fact capable of fully facing a feared situation – and the anxiety that comes with it. Exposure allows us to clearly see what we fear and to learn that, just maybe, it is not as dangerous as we previously thought. But if you cannot see something clearly, it is very difficult to learn to think about it differently. Obviously, Elaine will have to take a plane on many occasions before her fear of flying can be completely *processed* (or "digested"): when it comes to exposure, once is clearly not enough. But by repeatedly taking the plane without neutralising, she is well on her way to extinguishing her fear and enjoying a greater quality of life.

In the previous example, we examined the effects of avoidance, neutralisation and functional exposure on a concrete fear, the fear of flying. Do these same principles apply to your worries? The short answer to that question is yes, they do. So returning to our original question: Why do some people worry constantly about terrible things that could happen, whereas others do not spend a lot of time dwelling on these possibilities? Because some people try to avoid or neutralise their worries, whereas others do not. How many times have you been told: "Just don't think about it." How many times have you tried to avoid thoughts about bad things that could happen? For many people with GAD, trying to avoid scary thoughts (and anxiety) is almost a way to life. As you now know, however, trying to avoid difficult emotions or thoughts does not work. In fact, trying to avoid worrisome thoughts can actually lead to an increase in these very same thoughts. This phenomenon is known as the *rebound effect*. Simply put, the rebound effect states that if you try to avoid or suppress an unwanted thought, you will tend to have this thought more often over the next few days. Think of throwing a ball against the wall. The harder you throw it, the faster it comes back to you. Trying to avoid or suppress an unwanted thought, like a worry, is much the same: the harder you try, the quicker and the more often it can come back to you.

The neutralisation of thoughts is a little more complex. We now know that people with GAD often tend to worry in "fuzzy ways." In other words, when they worry, they tend to do so without having clear and concrete thoughts about what they fear. This is a form of neutralisation (like reading a book to "forget" that one is waiting to board a plane). As we have seen previously, the best way to learn something new – and less threatening – about a feared situation is to see it clearly in all its detail. The clearer the picture, the more new learning can occur. What this implies is that by worrying in a fuzzy way (or on a superficial level), you will not be able to decrease your fear; rather, you will continue to worry without reaping any benefits from your "worrying work." A final point that needs to be addressed here is that people with GAD tend to not only worry in fuzzy ways, but also to jump from one worry to another. This is referred to as *chaining*. The problem with chaining is that it does not give you the opportunity to learn to think differently about what worries you. By constantly jumping from one worry topic to another ("I won't be able to retire at 65… my daughter will fail at school… my spouse will leave me"), you are not in a position to learn to think differently about your worries (in part because you simply do not have enough time to reflect on each topic). In summary, we know that people with GAD often

try to avoid their worries, and when they cannot, they tend to jump from one worry to another without clearly seeing what they are afraid of. Because of this, it is difficult for them to *re-evaluate* their fears. Hence the worrying continues…

As you may have guessed by now, the solution to this conundrum lies with functional exposure. By systematically and repeatedly exposing yourself to clear and concrete thoughts of what you fear, you will be in a position to develop new ways of thinking about your fears. In our experience, the best way to do this is to use writing to assist you in making your fears more concrete, detailed and imaginable. Thus, we will use written exposure to help you with your worries about potential problems. How does that sound?

The first step of written exposure involves the identification of a target worry. The therapist should encourage the client to select his most distressing worry. If the client is not willing to do so, he should select a slightly less distressing worry. Once the target worry has been identified, the client will be asked to write about his feared outcome for 30 minutes. It is of the outmost importance that the first written exposure session takes place at the clinic. The therapist will need to manage session time to ensure that the client has sufficient time to write for 30 minutes and be debriefed following the exposure session. Before the first exposure session, the therapist should present the following guidelines for written exposure:

- *The scenario should be written in the first person, present tense (to increase the client's "proximity" to the feared outcome).*
- *The scenario should depict the client's worst-case scenario (e.g., loved one dying in a car accident).*
- *The scenario should be devoid of avoidance and neutralisation.*
- *The scenario should include as many sensory elements (e.g., sights, sounds, smells) as possible (to increase the scenario's vividness, concreteness and "imaginability").*
- *The scenario should include a description of the client's emotional reaction to the feared situation (to foster emotions during the writing session).*
- *The scenario should be "frightening", but believable.*
- *The scenario should aim to primarily provoke feelings of anxiety (and not sadness).*

In addition to the above guidelines, the therapist will want to mention that there is only one procedural rule for written exposure: to write continuously for 30 minutes at a moderate pace. The client should not be concerned about grammar or spelling mistakes; in fact, concern about writing form will only make the scenario less emotionally evocative. Rather, the client should describe the scenario as it comes to mind, as he would describe it verbally to someone else. The therapist will also want to remind the client that the first exposure session is a learning experience. The client should keep in mind that writing about a worst-case scenario without neutralising is not an easy thing to do at first. With practice, however, he should be able to fully develop this new skill.

Following the initial written exposure session, the therapist should expect to take 10-15 minutes to debrief with the client. The therapist will first want to review the general exposure procedures to identify any problems that may have come up. For example, if the client did not experience any anxiety while writing about the feared outcome, the scenario may need to be modified in some way. Next, the therapist and client should review the written scenario and look for signs of avoidance or neutralisation ("Is there anything in your scenario that makes it less threatening?"). Finally, the therapist will want to consolidate any new learning made during the writing session by asking the client if the scenario now seems less probable, less catastrophic or more manageable. In some cases, the therapist may also want to ask the client if the meaning ascribed to the feared outcome has changed (e.g., can the client begin to integrate the feared outcome into his "philosophy of life?").

Between-Session Exercises

Following the initial exposure session, the client is ready to begin conducting written exposure at home, as a between-session exercise. The client should conduct at least three sessions per week for the remainder of this treatment module. Obviously, the greater the number of exposure sessions, the greater the potential benefit. Each home written exposure session involves writing about the feared outcome for 30 minutes, following the guidelines described above. Exposure at home is ideally carried out in the early evening, not too close to bedtime so as not to interfere with sleep onset. The client should continue to target the same feared outcome until it no longer provokes an anxious response. Of note, each writing session provides an opportunity for the client to delve deeper into the scenario and to incorporate new elements that may increase its vividness, concreteness and imaginability.

There are two forms that accompany home exposure. The first is the Scenario for Exposure form, which the client can use to write the scenario (and be reminded of the principles of written exposure). The second is the Exposure Summary form. This second form allows the client to consolidate new learning by estimating the probability, cost and manageability of the feared outcome after each written exposure session.

Scenario for Exposure

Name: Date: Therapist:

Please keep in mind the following principles when writing your exposure scenario:

- The scenario should be written in the first person, present tense.
- It should depict your worst-case scenario.
- It should not contain elements of avoidance and neutralisation.
- It should include as many sensory elements (e.g., sights, sounds, smells) as possible.
- It should include a description of your emotional reaction.
- It should be frightening, but believable.
- It should provoke feelings of anxiety.

Worst-case Scenario

Exposure Summary

Name: Date: Therapist:

Theme of scenario: _____

To complete before exposure:

1. Time:

2. What is your current level of anxiety about your worst-case scenario?

   Rate from 0 (no anxiety) to 100 (extreme anxiety): _____

To complete after exposure:

1. Time:

2. What is your current level of anxiety about your worst-case scenario?

   Rate from 0 (no anxiety) to 100 (extreme anxiety): _____

3. What is the probability that your worst-case scenario will actually happen?

   Rate from 0 (no probability) to 100 (extreme probability): _____

4. How catastrophic would it be if your worst-case scenario actually happened?

   Rate from 0 (not catastrophic) to 100 (extremely catastrophic): _____

5. To what extent would you be able to deal with (or manage) your worst-case scenario if it actually happened?

Rate from 0 (not at all) to 100 (completely): _____

Module 6
Relapse Prevention

Following therapy it will be important to become your own therapist in order to maintain your gains; in this way you can prevent your worries from diminishing your quality of life. Becoming your own therapist signifies correcting your beliefs that relate to worry. This also involves the application of strategies like imaginal exposure or problem solving as soon as you experience worry that you consider excessive. Being your own therapist also implies regularly evaluating your method of reacting to worries, encouraging yourself to persevere even when it's difficult, and congratulating yourself for both your large and small successes.

It is important to keep in mind that there is a significant difference between a *lapse* (normal fluctuations in anxiety levels) and a *relapse*. To experience an increase in worrying from time to time is normal, and is not necessarily a relapse. An individual's reaction to an increase in worry is an important factor. In fact, experiencing a slight increase in worrying for a few days can be seen as a "problem", but the problem is not dramatic and the reaction that you have in response to this problem has a good chance of influencing the duration of the worry period being experienced. For example, two individuals worry a lot during a three-day period. In the middle of the week, the first individual realizes that an accumulation of work has been causing his stress and worry. He tells himself that he will try to finish his excess workload as soon as possible, within reason, and will relax on the weekend. He can always work for two hours on Sunday morning if he hasn't finished by Friday. By the end of the week he is finished his work and is satisfied and relaxed. The second individual is also stressed and worried because of an accumulation of work. He does all that he can to finish but is not very optimistic about finishing by Friday. By Friday at 5 o'clock the individual has finished his work and says: "What a crazy week! I am never able to get through a surplus of work without worrying about it all week! It took all my energy. What will it be like the next time? I won't be able to do it!"

Obviously there will be moments when you will be more susceptible to high levels of worry and anxiety. Remember that many situations have this effect on most people. These situations include periods when you have many responsibilities, when you are tired, when you feel "down", or simply at different times of the week or year. It is important that you identify these situations so that you will not be caught off guard when you begin to feel more worried and anxious. By having realistic expectations, you will be in a position to deal with difficult situations as they come up. These difficult periods can be seen as an opportunity to try the new strategies you learned during your therapy. The fact that you continue to experience worry from time to time simply gives you the opportunity to try the newly learned strategies that will give you a better chance at long-term protection against excessive worrying that can drain your quality of life.

One final point should be emphasized. Moderate levels of worry and anxiety are a normal part of life. Everyone worries and feels anxious from time to time, including therapists. The goal of this therapy was to help you to alter certain thoughts, behaviours and emotions so that you would no longer constantly experience excessive and uncontrollable worry and anxiety. If you feel that your worry and anxiety are now manageable, you have made wonderful progress. Congratulations!

Appendix 14 Therapy Components Checklist

THERAPY COMPONENTS CHECKLIST

The attached is a list of topics which would normally be covered during a course of CBT in GAD in an IAPT setting. Some will be presented by the client; others must be specifically sought and may be appropriate for discussion earlier or later during CBT, depending on the individual circumstances. You are being asked to fill this in as it is helpful for us to keep a record of the components that have been covered during CBT.

Instructions for Use

After each CBT session, please go through the checklist and indicate what topics were covered and when by marking a tick under the corresponding session number. If a topic is re-visited in another session, please indicate this by ticking all sessions the topic/component is covered in. If any topics are deliberately excluded (e.g. by negotiation with the client), please indicate the reasons for this in the comments box. The individual components of the checklist have been placed into sections for convenience. However the division of these is somewhat arbitrary. For example behavioural techniques may be associated with cognitive change and cognitive change may be associated with new behaviours.

Where appropriate these areas should be covered during the course of therapy. However we are not seeking a 'cookbook approach' and therefore this list should be considered a guide rather than a requirement.

Patient ID: Therapist Initials:

Session the component was covered:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
General Procedures																
Initial assessment																
Psychoeducation on GAD																
Explain Dugas CBT model																
Present a shared formulation																
Eliciting patient feedback																
Goal setting in therapy session																
Review of shared formulation																
Between session exercises (homework)																
Checking that the patient has understood																
Relapse prevention																
General CBT techniques																
Elicited key cognitions																
Identified key emotions																
Elicited key behaviours																
Use of guided discovery																
Psycho-education and worry awareness																
Normalised worry																
Explored types of worries																
Engaged in worry awareness training																
Evaluation of the usefulness of worry																
Explore the usefulness of worry																
Role played lawyer/prosecutor																
Uncertainty recognition/ exposure																
Behavioural exposure to uncertainty																
Strategies for dealing with uncertainty																
Dropping safety behaviours																
Problem solving																
Problem orientation																
Problem definition and goal formulation																
Brainstorming alternatives																
Decision making																
Solution implementation																
Written exposure																
Did you undertake written exposure																
Was the present tense used																
Depiction of the worst case scenario																
Included a variety of senses																
Included the emotional reaction																
Use of Specific GAD forms																
Worry diary																
Beliefs about worry																
Advantages/disadvantages of worry																
Manifestations of intolerance to uncertainty																
Exposure to uncertainty																
Recurrent problems checklist																
Resolution of a problem																
Scenario for exposure																
Exposure summary																

Appendix 15 End of Therapy Checklist

End of Therapy Checklist (EoTC) Therapist Initials:…… Participant ID:……..

Date of completion ……

Please take some time to fill in the following when the client has **completed therapy altogether**:

Adherence score:

Was the following undertaken:	Yes	No
Psycho-education and worry awareness work	☐	☐
Evaluation of the usefulness of worry	☐	☐
Uncertainty recognition/exposure	☐	☐
Problem Solving	☐	☐
Written Exposure	☐	☐

Adherence according to the self-report measure requires that at least 3 out of 5 of the above are covered

(a) What were the 3 most important aspects of the therapy and why?

1. _____
_____
_____

2. _____
_____
_____

3. _____
_____
_____

(b) Was there anything you felt was missing from this therapy?

_____
_____
_____

c) General comments

(d) Were any of the following covered during any of the sessions:

	Yes	No
Please note the following methods are NOT PERMITTED. Please note if they were nevertheless used in treatment, at what session and the reason they were used.		
Passively listening	☐	☐
Using psycho dynamic interpretation	☐	☐
Using relaxation, meditation, yoga	☐	☐
Avoiding thoughts (e.g. not thinking about worries, or saying "stop")	☐	☐
Reassurance (e.g. from friends, family or professionals, etc.)	☐	☐
Avoid triggers (e.g. not going to places that trigger concerns)	☐	☐
Mindfulness	☐	☐
Acceptance based interventions	☐	☐
Using a worry tree	☐	☐
Controlled worry periods	☐	☐

Appendix 16 Relapse prevention sheet

CBT for GAD – Relapse Prevention Sheet Therapist Initials:… Participant ID:……

1. Worry Diary

Was keeping a worry diary useful?

_____

What were my main worry themes during treatment?

_____

_____

2. Positive Beliefs about Worry

Which of the 5 positive beliefs applied to me before treatment?

_____

_____

What do I believe now?

_____

_____

3. Intolerance of Uncertainty

What were my main behavioural manifestations of intolerance of uncertainty?

What items did I put on my exposure hierarchy?

4. Problem Solving

Before treatment, in what ways did I have a negative problem orientation?

Was applying the problem solving steps useful?

What do I need to remember?

5. Written Exposure

For which hypothetical situation(s) did I use written exposure?

What did I learn from using written exposure?

6. Looking Ahead

In the future, what situations might increase my worry or trigger a relapse?

How would I know? What would be the early signs?

Where do I want to be in 12 months' time in terms of my worry and anxiety?

How will I achieve my long-term goals?

What are the most important things I need to remember?

EME
HS&DR
HTA
PGfAR
PHR

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