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Protocol version history

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2	4th May 2017	Rebecca Gould	Feedback from the Research Ethics Committee with respect to Phase 1 of the study
3	5th July 2017	Rebecca Gould	Recommended changes following review by sponsor for HRA approval for Phases 2 and 3 of the study
4	13th November 2017	Rebecca Gould	Recommended changes following review by the Study Steering Committee, Project Development Group & the Funder

Signatures

The Chief Investigator and the JRO have discussed this protocol. The investigator agrees to perform the investigations and to abide by this protocol.

The investigator agrees to conduct the trial in compliance with the approved protocol, the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the current Research Governance Framework, the Sponsor's SOPs, and other regulatory requirements as amended.

Chief Investigator		10.03.17
Dr Rebecca Gould		
UCL	Signature	Date

Sponsor		10.03.2017
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List of abbreviations

ACT	Acceptance and Commitment Therapy
CBT	Cognitive Behavioural Therapy
CMHT	Community Mental Health Team
CRF	Case Report Form
CRN	Clinical Research Network
GAD	Generalised anxiety disorder
GCP	Good Clinical Practice
HRA	Health Research Authority
IAPTs	Improving Access to Psychological Therapies services
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
ISRCTN	International Standard Randomised Controlled Trial Number
PMG	Project Management Group
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SSC	Study Steering Committee
UCL	University College London

1 Trial personnel

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2 Summary

Objectives:	The primary objective of the study is to develop and refine a manualised intervention based on Acceptance and Commitment Therapy (ACT) for treatment-resistant generalised anxiety disorder (GAD) in older people in accordance with MRC guidelines for developing and evaluating complex interventions (MRC, 2008). The secondary objectives are to: i) assess the feasibility and acceptability of the intervention via an open uncontrolled feasibility study in order to inform a future substantive trial of clinical and cost-effectiveness; ii) use a nationwide survey to clarify usual care for treatment-resistant GAD in older people; and iii) clarify key study design parameters for a future substantive trial.
Trial design and methods:	Individual qualitative interviews to develop the intervention in Phase 1. Open uncontrolled feasibility study assessing the acceptability and feasibility of ACT for treatment-resistant GAD in older people using quantitative and qualitative methods in Phase 2. Primary outcome measures will be acceptability (session engagement and satisfaction with therapy) and feasibility (recruitment and retention). Individual qualitative interviews with participants and therapists will further assess acceptability and feasibility.
Trial duration per participant:	6 months in Phase 1 and 20 weeks in Phase 2
Estimated total trial duration:	24 months
Planned trial sites:	Multi-site
Total number of participants planned:	15 in Phase 1 and 40 in Phase 2
Main inclusion/exclusion criteria:	Inclusion criteria: 1. Older people aged 65+ with a primary diagnosis of GAD as determined by the MINI International Neuropsychiatric Interview (Sheehan et al., 1998) and the Structured Clinical Interview for DSM-IV Axis II Disorders (First et al., 1995, 1997); 2. Failed to respond to treatment in Steps 1-3 of the stepped care approach for GAD; 3. Living in the community; 4. Able to provide informed, written consent; 5. Sufficient understanding of English to enable them to engage in ACT and complete patient-reported outcome measures; 6. In Phase 2 only: Have not participated in qualitative interviews in Phase 1 of the project. Exclusion criteria: 1. Diagnosis of dementia; 2. Standardised Mini-Mental State Examination (Molloy et al., 1991) score of <25; 3. Currently receiving ongoing psychotherapy or who are unwilling to refrain from engaging in other forms of psychotherapy during the receipt of ACT; 4. Suicidal ideation with active intent for whom an inpatient admission would be more appropriate; 5. Other medical or psychosocial factors that could compromise full study participation such as imminently life-limiting illness or severe sensory deficits (e.g. blindness); 6. Intellectual disabilities.
Statistical methodology and analysis:	In Phase 1 and 2, qualitative data will be transcribed verbatim and analysed iteratively using thematic analysis In Phase 2, binary and other categorical measures will be summarised using frequencies and percentages, and continuous measures using means and standard deviations (or medians and interquartile ranges for very skewed distributions). Change in patient-reported outcome measures between 0 and 20 weeks will be estimated using

multilevel linear or logistic regression models with a random effect of person to account for the repeated measures on individuals over time. The precision of estimates will be assessed using 95% confidence intervals.

3 Background and rationale

The problem: GAD is the most common anxiety disorder in older people, with prevalence rates estimated to range from 1.2% to 11.2% (Wetherell et al., 2005; Wolitzky-Taylor et al., 2010). GAD in older people is associated with poorer health-related quality of life, increased disability, greater healthcare utilization, and functional limitations in comparison to non-anxious older people (Goncalves et al., 2012; Porensky et al., 2009; Wetherell et al., 2004). Comorbidity with other anxiety, mood and personality disorders is common (Beekman et al., 2000; Cairney et al., 2008; Schaub et al., 2000; van Balkom et al., 2000), and is associated with even poorer outcomes. For example, comorbid anxiety and depression is associated with more severe somatic symptoms, poorer social functioning, greater suicidal ideation, and greater prescription of benzodiazepines, as well as poorer treatment response (Bystritsky, 2006; Lenze et al., 2001). Several factors are associated with treatment-resistant anxiety including comorbid physical and mental health conditions, noncompliance, and environmental stressors (Bystritsky, 2006).

How GAD is currently managed: National Institute for Health and Clinical Excellence guidelines (2011) currently recommend a stepped care approach to the management of GAD. Step 1 comprises identification and assessment, followed by education and active monitoring within primary care. If symptoms have not improved then it is recommended that one or more low-intensity psychological interventions such as guided self-help based on cognitive behavioural therapy (CBT) and psychoeducational groups are offered (Step 2), again within primary care. Should symptoms persist or if there is marked functional impairment then it is recommended that pharmacotherapy (e.g. selective serotonin reuptake inhibitors) and/or high-intensity, individual psychotherapy (either CBT or applied relaxation) are offered (Step 3). Following this, if symptoms still persist then a referral to specialist mental health services (usually located within secondary care) for assessment and treatment is recommended in Step 4. Recommended treatment options in Step 4 include offering interventions from Steps 1-3 that have been previously declined and offering combination therapy. Although there is no agreed definition of treatment-resistant GAD (Lanouette et al., 2013), when GAD fails to respond to treatment after completing the first three steps of this approach then it can be thought to be resistant to treatment. Guidance on managing this in older people (and indeed in working age people) is lacking.

How the problem will be addressed: A manualised psychotherapy intervention based on ACT and the acceptance model of GAD (Hayes et al., 1999; Roemer et al., 2002, 2005) will be developed specifically for older people with treatment-resistant GAD in Phase 1 of the project. The feasibility and acceptability of delivering the intervention to this population within the NHS will be assessed in an open uncontrolled feasibility study in Phase 2.

Why ACT is being proposed: ACT is an acceptance-based behaviour therapy (Hayes et al., 1999) that is a novel alternative to conventional forms of psychotherapy such as CBT. It aims to reduce attempts to control, eliminate or avoid negative thoughts, emotions and sensations, and to improve function through increased engagement in valued, meaningful activities. Conventional CBT, on the other hand, aims to change or suppress emotional experiences, for example, by challenging the validity of negative thoughts or trying to eliminate or solve problems. The difficulty with this approach is that many older people with treatment-resistant GAD experience multiple comorbid chronic physical and mental health conditions, as well as multiple losses (e.g. to one's health, family, social network, role/identity, and financial status). Such comorbidities and losses may not be amenable to change with conventional CBT strategies (e.g. problem solving and thought challenging), even if adapted for older people. Furthermore, challenging the validity of worries about future losses may be perceived negatively by older people when, although these are excessive and unhelpful, they may have an obvious basis in reality. In addition, there is evidence that control-orientated strategies such as trying to eliminate problems that cannot be solved is actually detrimental to older people's wellbeing (Isaacowitz et al., 2002). In contrast, ACT, with its focus on increasing adaptive functioning and how best to live with such difficulties and worries (as opposed to challenging, changing or trying to eliminate them), may be more appropriate and successful in this population. Supporting this, ACT has been shown to better fit the needs of people with disabling long-term conditions (Kangas et al., 2011), and may be particularly helpful where distress is associated with realistic or valid thoughts (Jourdain et al., 2009). Furthermore, preliminary evidence suggests that ACT is acceptable to older people including those with GAD, advanced cancer and chronic pain (Alonso-Fernández et al., 2015; Serfaty et al., 2014; Wetherell et al., 2011a, 2011b).

Why ACT is being proposed rather than other interventions: Other interventions that could be considered for the management of treatment-resistant GAD include further or more intensive conventional CBT, applied relaxation, and collaborative care. ACT is considered to be the treatment of choice over these interventions for a number of reasons. First, GAD may not respond to conventional psychotherapy (e.g. CBT or applied relaxation) due to: i) failure of the person to use the therapeutic skills they have been taught; ii) failure of the learned therapeutic skills to reduce distress, even when they have been put into practice by the person; or iii) the person's refusal or failure to engage with therapy (e.g. due to a lack of fit between the person and the therapeutic approach or therapist). Consequently, offering further conventional CBT or applied relaxation to those with treatment-resistant GAD, even if augmented or adapted for older people, may lead to yet more inadequate treatment response or refusal. Secondly, ACT and ACT-based approaches have been shown to be as effective as CBT and applied relaxation for GAD (Avdagica et al., 2014; Clarke et al., 2014; Hayes-Skelton et al., 2013; Roemer et al., 2008; Wetherell et al., 2011a; Zargar et al., 2012), but have advantages over conventional CBT through improved engagement and retention (Clarke et al., 2014; Wetherell et al., 2011a). Thirdly, control-orientated strategies used in CBT and applied relaxation may actually be detrimental to older people for reasons

noted above. Finally, there is evidence that a collaborative care intervention in which people were given the choice of CBT, pharmacotherapy or both was found to be no more effective than usual care in older people with GAD (Wetherell et al., 2013).

Why this research is needed now: A recent HTA systematic review was unable to identify any randomised controlled trial (RCT) or prospective comparative study of any intervention for treatment-resistant anxiety in older people (Barton et al., 2014). Thus, examination of the broader literature on psychological interventions for GAD in older people is required. Most studies have focused on CBT (Brenes et al., 2015; Jones et al., 2015; Mohlman et al., 2003, 2005; Stanley et al., 1996, 2003, 2009, 2014; Wetherell et al., 2003, 2009, 2011, 2013), with a few examining other psychological interventions (ACT [Wetherell et al., 2011a] and Mindfulness-Based Stress Reduction [Lenze et al., 2014]). Pooled odds ratios in favour of these interventions when compared with waiting list or usual care controls, but not when compared with active controls or other forms of psychotherapy have been reported (Goncalves et al., 2012).

There is evidence that CBT is less effective and less acceptable to older people compared to younger people. In a meta-analysis of CBT for late-life anxiety disorders, small-to-moderate effect sizes were reported that were smaller than those found in younger people (Gould et al., 2012). Smaller effect sizes in favour of CBT for GAD, as well as higher dropout rates, have also been reported in older people compared to younger people (Covin et al., 2008; Hunot et al., 2007). Furthermore, there is evidence that older people access Improving Access to Psychological Therapies services less than younger people (Royal College of Psychiatrists, 2013), which could indicate that CBT approaches are perceived as less acceptable to them by clinicians or indeed by older people. Thus, there is a need to find an alternative form of psychotherapy that is effective and acceptable in this population. Evidence suggests that older people with chronic pain are more likely to clinically respond to ACT than CBT, whereas younger people are more likely to respond to CBT (Wetherell et al., 2015), and so ACT may be a particularly promising candidate for this age group.

ACT has been applied to a wide range of mental and physical health conditions including anxiety, depression, and chronic pain (Sharp, 2012; Smout et al., 2012). However, very few studies of ACT have been conducted with older people. The majority of studies have examined ACT for chronic pain (Alonso-Fernandez et al., 2013, 2015; McCracken et al., 2012; Wetherell et al., 2011b), with other studies focusing on GAD (Wetherell et al., 2011a), veterans aged 65+ with depression (Karlin et al., 2013), and those living in long-term care facilities (Davison et al., 2016). Beneficial effects on symptoms of depression, anxiety and functional measures have been reported in these studies, along with high rates of attendance. For example, 100% session attendance was reported in 7/7 older people with GAD (Wetherell et al., 2011a) and in 59/76 older people with depression (Karlin et al., 2013). An ongoing RfPB-funded study of ACT in palliative care (Serfaty et al., 2014) additionally suggests good uptake rates in older people with advanced cancer (with 9 out of 17 being aged 65 years+), as well as good engagement with ACT.

With respect to the use of ACT in GAD and treatment-resistant disorders, it has been found to be as effective as cCBT and applied relaxation in the treatment of GAD (Avdagica et al., 2014; Clarke et al., 2014; Hayes-Skelton et al., 2013; Roemer et al., 2008; Wetherell et al., 2011a; Zargar et al., 2012), but more effective in terms of treatment completion and dropout rates (Clarke et al., 2014; Wetherell et al., 2011a). A preliminary RCT of ACT vs. CBT for all forms of GAD in older people reported improvements in worry/anxiety and depression with both interventions, but higher treatment completion rates with ACT (Wetherell et al., 2011a). While these results are promising, this study is limited by its small sample size (N=7 in the ACT condition and N=9 in the CBT condition) and limited applicability to older people with treatment-resistant GAD in the UK (as the study did not exclusively recruit older people with treatment-resistant GAD and was conducted in the US). Lower dropout and greater recovery rates with ACT vs. CBT in the management of people with treatment-resistant mental health problems including anxiety, depression and personality disorders, who had previously received at least eight sessions of psychological therapy, have been demonstrated (Clarke et al., 2014). However, the mean age of participants in this study was 43.5 years and it did not specifically include those with treatment-resistant GAD. Thus, overall, there are several compelling justifications for an alternative form of psychotherapy that sufficiently meets the needs of older people with treatment-resistant GAD. ACT shows greatest promise as this alternative form, but has not yet been applied to this target population, and so it is the feasibility of this approach that will be examined in this study.

3.1 Assessment and management of risk

Information sheets will provide participants with information about the possible benefits and risks of taking part in the study. Participants will be given the opportunity to discuss this with the researcher prior to consenting to the study.

Risk: Participants will remain under the care of their GP/consultant psychiatrist/care coordinator for the duration of the open uncontrolled feasibility study. Risk of harm to self or others will be monitored throughout the study. If suicidal ideation without intent is expressed at any point then the participant's GP/consultant psychiatrist/care coordinator will be contacted and the participant will continue to be monitored weekly. If suicidal ideation with active intent is expressed at any point then the participant's GP/consultant psychiatrist/care coordinator will be contacted and the participant will be referred for urgent psychiatric assessment. The decision as to whether the participant should be withdrawn from the study will depend on the outcome of this assessment, and in full discussion with the participant and clinical team.

Inadequate treatment response: If a participant remains moderately to severely anxious or depressed after receiving ACT (as indicated by a score of >8 on the Geriatric Depression Scale or >11 on the Geriatric Anxiety Inventory) then this will be discussed

with the participant and appropriate action will be taken (e.g. their GP/consultant psychiatrist/care coordinator will be contacted and the participant will be referred for further psychotherapy or medication review).

Potential distress: Any distress experienced during qualitative interviews will be identified and responded to by the research assistant, under the supervision of the Chief Investigator. Evidence of any adverse effects from the ACT intervention will be monitored throughout the feasibility study. Reasons for withdrawing participants from the ACT intervention (e.g. if participants require immediate inpatient treatment) will be discussed with the Project Management Group prior to the commencement of the feasibility study. Anyone experiencing an increase in distress will be assessed for risk and standard operating procedures will ensure safety is respected. New reports of suicidal behaviour during the ACT intervention will be reported as Serious Adverse Events.

Lone working: All staff seeing participants in their own homes (e.g. therapists, research assistant) will follow local procedures for lone working in the community, including ensuring that a diary system is implemented to monitor movements and 'checking in' with a central administrator after sessions to confirm one's safety.

4 Trial objectives

Primary: The primary objective of the study is to develop and refine a manualised intervention based on ACT for treatment-resistant GAD in older people in accordance with MRC guidelines for developing and evaluating complex interventions (MRC, 2008).

Secondary: The secondary objectives are to:
i) Assess the feasibility and acceptability of the intervention via an open uncontrolled feasibility study in order to inform a future substantive trial of clinical and cost-effectiveness;
ii) Use a nationwide survey to clarify usual care for treatment-resistant GAD in older people;
iii) Clarify key study design parameters for a future substantive trial.

5 Trial design

Individual qualitative interviews to develop the intervention in Phase 1. Open uncontrolled feasibility study assessing the acceptability and feasibility of ACT for treatment-resistant GAD in older people using quantitative and qualitative methods in Phase 2.

6 Selection of participants

6.1 Inclusion criteria

1. Older people aged 65+ with a primary diagnosis of GAD as determined by the MINI International Neuropsychiatric Interview (Sheehan et al., 1998) and the Structured Clinical Interview for DSM-IV Axis II Disorders (First et al., 1995, 1997);
2. Failed to respond to treatment in Steps 1-3 of the stepped care approach for GAD (e.g. 6 weeks of an age-appropriate dose of antidepressant medication or a course of individual psychotherapy), those who have failed to tolerate this treatment, or those who have previously refused this treatment and are still symptomatic. When determining whether a person has failed to respond to treatment for GAD, if they have remitted and then relapsed in relation to GAD then any treatment received prior to remission will not be considered when deciding whether they meet criteria for treatment resistance;
3. Living in the community;
4. Able to provide informed, written consent;
5. Sufficient understanding of English to enable them to engage in ACT and complete patient-reported outcome measures;
6. In Phase 2 only: Have not participated in qualitative interviews in Phase 1 of the project;
7. In Phase 2 only: A minimum of 1 month interval between previous psychotherapy and engagement in ACT.

6.2 Exclusion criteria

1. Diagnosis of dementia;
2. Standardised Mini-Mental State Examination (Molloy et al., 1991) score of <25;
3. Currently receiving ongoing psychotherapy or who are unwilling to refrain from engaging in other forms of psychotherapy during the receipt of ACT;
4. Suicidal ideation with active intent for whom an inpatient admission would be more appropriate;
5. Other medical or psychosocial factors that could compromise full study participation such as imminently life-limiting illness or severe sensory deficits (e.g. blindness);
6. Intellectual disabilities.

It is common to include a psychotropic drug stabilisation period (e.g. a stable dose for at least two months) as one of the inclusion criteria in psychotherapy studies to allow for spontaneous recovery, and to control for the potential confound of pharmacotherapy on mental wellbeing. However, this will not be included in the current feasibility study for two reasons. First, spontaneous recovery in those who have not responded to Steps 1-3 of the stepped care approach for GAD is unlikely. Secondly, it is likely that a drug stabilisation period would have a significantly negative impact on recruitment as many potential participants would either be ineligible to take part or unwilling to wait for drug stabilisation to occur before receiving psychotherapy. Service users are frequently referred to Community Mental Health Teams (CMHTs) for medication reviews, which usually entails switching to

another drug, adding in another drug, or changing drug doses, and so it can take a number of months before a stable dose is achieved. Instead of including a psychotropic drug stabilisation period, all drug use will be monitored during the course of therapy, and will be accounted for in subsequent data analyses.

6.3 Recruitment

Recruitment procedures: Potential participants will be recruited via self-referral from the community, referrals from primary and secondary care settings (GP surgeries in North Thames Clinical Research Network [CRN], South London CRN and Thames Valley and South Midlands CRN, and Improving Access to Psychological Therapies services [IAPTs] and CMHTs for older people in Camden and Islington NHS Foundation Trust, South London and Maudsley NHS Foundation Trust, Barnet Enfield and Haringey Mental Health trust and Oxford Health NHS Foundation Trust), and GP list searches. In addition, recruitment via self-referral from the community and via referrals from primary and secondary care settings in Oxfordshire will occur in Phase 1. GP practices will be recruited from local Clinical Research Networks and local contacts. To facilitate self-referral, leaflets, posters and advertisements will be distributed in GP surgeries and other community settings such as luncheon clubs and activity groups for older people. Leaflets will include the Generalized Anxiety Disorder-7 (Spitzer et al., 2006), a brief 7-item screening tool, and potential participants will be invited to contact the research team if they score >= 11 on this scale (corresponding to moderately severe GAD and above). Eligibility of potential participants with respect to the criterion for treatment-resistant GAD will be confirmed, with consent, from GP medical records by clinical specialists from the research team. Those who fail to meet this criterion will be signposted to IAPTs.

Potential participants from primary and secondary care settings will be identified and approached about the study in one of three ways. First, clinicians from GP surgeries, IAPTs and CMHTs will identify and approach potentially eligible participants and seek verbal consent for researchers to contact them. Older people who meet diagnostic criteria for GAD are frequently referred to IAPTs and CMHTs with a diagnosis of major depression and comorbid anxiety rather than GAD. Consequently, clinicians in these services will be asked to screen service users who are referred with a diagnosis of major depression and comorbid anxiety for GAD using the Generalized Anxiety Disorder-7 (Spitzer et al., 2006). For any service user scoring 11+ on this scale (corresponding to moderately severe GAD and above), clinicians will ask the service user which symptoms are most distressing, severe or of most concern to them. If symptoms of GAD are most distressing, severe or of most concern to them, or if symptoms of GAD and depression are equally problematic, then the clinician will discuss the study with them and seek verbal consent for researchers to contact them. If symptoms of depression are most distressing, severe or of most concern to them then the clinician will refer them for appropriate treatment. Secondly, people who have already provided consent for contact will be identified by clinicians but then contacted by a Band 5 clinician. Thirdly, nurses or GPs within participating GP practices (i.e. those who have expressed an interest in participating in research through primary care research networks and local contacts) will, with support from the research team, conduct searches of their electronic medical records to identify those with diagnoses of GAD and other chronic anxiety states using a broad list of Read codes (Walters et al., 2012), a hierarchical coding system used to record clinical information such as diagnoses. This will be supplemented by adding an alert and simple referral template to the software systems of participating GP practices that pops up whenever a diagnosis of GAD (with or without terms such as 'chronic anxiety' and 'anxiety state') is entered by a participating GP (identified through the Clinical Research Networks) for a person aged >= 65yrs. Strategies involving identifying participants through GP list searches are ones that have been successfully employed in previous studies (e.g. Buszewicz et al., 2016; Osborn et al., 2016). Once potentially eligible participants have been identified through electronic medical record searches, nurses or GPs within participating GP practices will approach them and seek verbal consent for researchers to contact them. Postal invitations may be sent out to identified potentially eligible participants by nurses or GPs within participating GP practices. Potentially eligible participants will only be contacted by the research team if they contact the research team following receipt of the letter. In addition to the above, the study will be promoted through talks and presentations at local community groups (e.g. luncheon clubs and activity groups), to GPs, in team meetings in IAPTs and CMHTs, and via online mental health forums. Once potential participants have been identified and verbal consent for contact has been obtained, they will be contacted via telephone by a member of the research team. The study will be described to them and any questions or concerns will be discussed. If they express an interest in participating in the study then they will be sent an information sheet and invitation letter, with their consent. They will then be contacted a minimum of 48 hours later by a member of the research team to determine whether they are still interested in participating in the study. If they are, then an appointment for a screening interview (lasting 1.5 hours) will be arranged with a member of the research team. Written informed consent will be sought from potentially eligible participants by a Band 5 clinician, research nurse or research assistant during this screening interview, after which eligibility for inclusion in the study will be determined.

Participant recruitment at a site will only commence when the trial has:

1. Been confirmed by the Sponsor (or its delegated representative);
2. Received Health Research Authority (HRA) approval;
3. Received confirmation of capability and capacity.

6.4 Informed consent

Participants would be expected to be able to provide informed consent for participation, provided that appropriate time and care has been taken by the Band 5 clinician, research nurse or research assistant to explain the research, and they had sufficient time to make a decision. It will be explained that participants are under no obligation to enter the study and that they can withdraw at any time, without having to give a reason and without their subsequent care being affected. It will be made clear to participants that no

disadvantage will accrue if they choose not to participate in the study. It is not expected that participants will lose the capacity to provide informed consent during the course of the study. If they do, then they will be withdrawn from the study. The initial giving of informed consent provides a clear indication of the person's likely perspective on continuing at this point. Current guidance from the British Psychological Society on evaluation of capacity when seeking consent will be followed, which is regarded as a continuing process rather than a one-off decision. Willingness to continue participating will be continually checked through discussion with participants during the study.

It is the responsibility of the Principal Investigator, or a person delegated by the Principal Investigator to obtain written informed consent from each participant prior to participation in the study, and following adequate explanation of the aims, methods, anticipated benefits and potential hazards. The person taking consent will be suitably qualified and experienced, and will have been delegated this duty by the Principal Investigator/Co-Investigator on the Staff Signature and Delegation of Tasks Log. Prior to recruiting participants, members of the research team will be provided with training in assessing capacity to consent to participate in research studies will be provided, if necessary. All potential participants will be given information sheets and will have the opportunity to discuss the study, ask questions and request further information at least 24 hours before being asked to provide verbal and written informed consent. Participants will be asked to provide consent in accordance with the Mental Capacity Act 2005. Participants will not be included in the project if they are unable to provide this. No study procedures will be conducted prior to the participant giving consent by signing the Informed Consent Form (ICF). Consent will not denote enrolment into the study. Screening and baseline assessments will only be completed after written consent is given. A copy of the signed ICF will be given to the participant. The original signed form will be retained in the study files at the co-ordinating site. The Participant Information Sheet and ICF will be reviewed and updated if necessary throughout the study (e.g. where new safety information becomes available) and participants will be re-consented as appropriate.

7 Interventions

7.1 Name and description of intervention under investigation

7.1.1 ACT

In ACT, psychological inflexibility, or the psychological suffering that emerges from experiential avoidance, cognitive fusion, loss of contact with the present moment, and failure to connect and act in accordance with one's values, is thought to underlie psychopathology (Hayes et al., 1999). There are six core clinical processes aimed at increasing psychological flexibility in ACT: i) acceptance - accepting or opening up to difficult or unpleasant emotional experiences rather than avoiding them; ii) cognitive defusion - stepping back or detaching from unhelpful thoughts, images and memories as opposed to being fused with them; iii) contact with the present moment - being in the here and now in contrast to ruminating about the past or worrying about the future; iv) self-as-context - observing oneself as distinct from the content of one's experiences; v) values - re-engaging with one's personal values and what matters rather than losing contact with them; and vi) committed action - committing to doing what matters in contrast to avoidance or inaction. Research has supported the applicability of these processes in a variety of clinical populations, including older people (Petkus et al., 2013).

The acceptance-based model of GAD (Roemer et al., 2002, 2005) draws on the ACT model in proposing four major components of GAD: i) internal experiences (i.e. thoughts, feelings and bodily sensations); ii) a problematic relationship with internal experiences (i.e. negatively reacting to internal experiences and fusion with these negative reactions); iii) experiential avoidance of internal experiences perceived to be threatening or negative (e.g. by worrying); and iv) behavioural restriction (i.e. reduced engagement in valued or meaningful actions). According to this model "individuals with GAD have negative reactions to their own internal experiences, and are motivated to try to avoid these experiences, which they do both behaviourally and cognitively (through repeated engagement in the worry process)" (Roemer et al., 2005, p216). Acceptance-based behavioural therapy (Roemer et al., 2005, 2007, 2008) addresses three main treatment components: i) psychoeducation about the acceptance-based model of GAD; ii) mindfulness and acceptance exercises aimed at increasing nonjudgemental awareness of internal and external experiences; and iii) achieving behaviour change through identifying and engaging in valued or meaningful actions. Evidence in support of this model, as well as acceptance-based behavioural therapy for GAD, has been reviewed by Behar et al. (2009). Further details about the intervention and its development are provided in Section 8.3.

7.1.2 Usual care

In addition to receiving ACT, all participants will receive usual care in Phase 2, which will be monitored using a short modified version of the Client Service Receipt Inventory that has been previously adapted for use in older people (Beecham et al., 1992; Serfaty et al., 2009). It is likely that usual care will comprise GP care with or without multidisciplinary team interventions including assessment, medication review and management, psychotherapy, occupational therapy, and case management. In addition to the Client Service Receipt Inventory, information will be extracted, with participants' consent, from GP medical records on GP and nurse consultations, prescribing and referrals in the 20 weeks before baseline and during the 20 weeks of receipt of ACT.

8 Trial procedures

8.1 Pre-intervention assessments

There are no specific pre-intervention assessments other than screening participants for inclusion criteria and conducting the baseline assessment. All pre-treatment procedures will be carried out as specified in the schedule of assessments (Appendix 4). Socio-demographic and clinical data collected at screening will include:

i) Age and presence of imminently life-limiting illness or severe sensory deficits;
ii) Psychiatric diagnoses using the MINI International Neuropsychiatric Interview (Sheehan et al., 1998) and the Structured Clinical Interview for DSM-IV Axis II Disorders (First et al., 1995, 1997);
iii) Previous and current treatment for GAD;
iv) Generalized Anxiety Disorder-7 (Spitzer et al., 2006): A brief screening tool consisting of 7 items scored on a 4-point scale;
v) Standardised Mini-Mental State Examination (Molloy et al., 1991): A brief 30-item cognitive screening tool;
vi) Suicidal ideation, intent and plans.

Additional socio-demographic and clinical data collected at baseline will include:
i) Sex, ethnicity, marital status, years of education, highest level of educational qualification, current occupation, and highest level of occupational attainment;
ii) Ongoing medication use including prescribed or illicit substances (dose and frequency) and length of current episode;
iii) Cumulative Illness Rating Scale-Geriatrics (Miller et al., 1992): A tool that measures current/chronic illnesses in the elderly.

8.2 Intervention procedures

8.2.1 ACT

Phase 1: Development of the intervention

In Phase 1, previously successful strategies (e.g. as used in START, MARQUE and CanACT; Livingston et al., 2014; Serfaty et al., 2014) will be used to develop a manualised intervention for treatment-resistant GAD in older people. Individual qualitative interviews will be conducted with an estimated 15 older people with GAD (or until saturation of possible responses to questions is reached i.e. no new themes are identified) who have previously been offered psychotherapy, some of whom have engaged and some of whom have not. Purposive sampling will be conducted on the basis of sex, age, socio-economic status and ethnicity to explore a range of perspectives. Interviews will explore individuals' attitudes towards their condition, its impact upon their lives, positive and negative experiences of psychotherapy, and facilitators and barriers to engagement in psychotherapy (including potential ways of overcoming barriers). They will also examine which elements of ACT interventions are considered suitable or relevant for older people and those that will require adaptation (for example, the choice of which metaphors to use in therapy), together with which general adaptations to therapy would be most helpful for older people (such as providing cognitive aids e.g. information sheets, handouts and appointment reminders to compensate for age-related cognitive difficulties). Participants will be recruited from London and Oxfordshire to obtain service user perspectives from those living within both inner city and more rural settings. Data from these interviews, together with discussions with experts in the field, will inform development of the intervention for treatment-resistant GAD in older people based on existing ACT approaches (Hayes et al., 1999) and the acceptance-based model of GAD (Roemer et al., 2002, 2005).

The intervention will address core clinical processes in ACT, as well as incorporate treatment components from the acceptance-based model of GAD, as outlined in Section 7.1, through modules focusing on: i) conducting an age-appropriate assessment that considers biological, psychological and social factors that have contributed to the development and maintenance of GAD; ii) developing a shared formulation or understanding of a person's current difficulties within the ACT model (e.g. determining how the core ACT processes are maintaining the person's current difficulties); iii) identifying core personal values and developing goals and actions in service of these; iv) providing psychoeducation about emotions, the ACT/acceptance-based models of GAD, the costs of control-orientated strategies, and the benefits of a more accepting, decentred stance; v) cognitive defusion and self-as-context exercises; vi) increasing non-judgemental emotional awareness and acceptance of one's experiences through mindfulness exercises; vii) committing to making behavioural changes in service of one's valued directions in life; and viii) relapse prevention (e.g. reviewing any gains made and ways of maintaining these). Each module will be associated with a specific set of skills, metaphors, experiential exercises and homework tasks designed to address core ACT clinical processes and hence increase psychological flexibility. Homework tasks will be set in collaboration with participants at the end of each session, and will be adjusted to accommodate physical health problems using 'selective optimisation with compensation' principles, as outlined below.

The intervention will be tailored to the needs of older people following age-appropriate augmented CBT and gerontological theory principles (Laidlaw et al., 2015), as well as recommendations for conducting ACT with older people (Petkus et al., 2013). The assessment will address key factors such as suicide risk and alcohol and drug misuse (including illicit and prescribed drugs) as they may interfere with therapy. A shared formulation will be developed within a lifespan context that takes into account biopsychosocial factors including medical comorbidities and functional impairments as these may influence therapy. Key ACT processes relevant to older people such as cognitive fusion with negative attitudes about ageing, chronic ill health, and physical or cognitive impairment will be fully explored and addressed as these may pose a barrier to behavioural change. 'Selective optimisation with compensation' principles of successful ageing will be used to help people achieve valued goals despite the challenges of ageing (e.g. by limiting goals to those that are most valued and using alternative strategies to compensate for those that are no longer available due to age-related difficulties; Alonso-Fernandez et al., 2013; Baltes et al., 1990). Mindfulness exercises will be incorporated in each session due to the difficulties that some older people experience in observing internal states (Petkus et al., 2013). Finally, standard therapeutic strategies will be used to compensate for age-related cognitive changes such as providing a workbook and session summaries (written in the person's own words) as a reminder of the content of the sessions, repeating key concepts and skills within and between sessions (e.g. recapping on the previous session at the beginning of the next session), working at a slower pace, and providing appointment reminders. It is important to compensate for mild age-related cognitive deficits as they have been associated with a reduced response to CBT in older people with GAD (Caudle et al., 2007).

Physical and mental health comorbidity including depression and mild cognitive deficits will be addressed throughout the intervention as this is common in treatment-resistant GAD and is associated with poor treatment response (Bystritsky, 2006). ACT was not developed with the treatment of specific disorders in mind, and so its transdiagnostic nature means that it will be uniquely placed to easily and efficiently address the range of presenting problems seen in elderly populations. The intervention will include a protocol for the use of inappropriate prescription medication (such as benzodiazepines and other hypnotic drugs), over-the-counter medication (such as sedative antihistamines), and illicit substances as these may interfere with therapy. The protocol will address psychoeducation about illicit or inappropriate drug use, the pros and cons of drug use, and ways of reducing drug use (e.g. via supervised gradual withdrawal augmented with psychotherapy as recommended in a recent meta-analysis [Gould et al., 2014]). If participants consent to reduce their use of illicit or inappropriate drugs then they will be invited to engage in a gradual withdrawal program, under supervision from their CMHT psychiatrist and/or GP, while engaged in ACT.

It is anticipated that the intervention will be delivered in 16 individual sessions, consistent with previous recommendations of 12-16 sessions of ACT for older people (Karlin et al., 2013; Petkus et al., 2013), as well as Step 3 of the stepped care approach for GAD (National Institute for Health and Clinical Excellence, 2011). Step 3 states that CBT or applied relaxation should usually consist of 12-15 sessions, with more sessions being offered if clinically required. The provision of 16 sessions will allow therapists to work at a slower pace, which is a recommended compensatory strategy for age-related cognitive changes in memory, attention and processing speed when working with older people (Boddington, 2014). An individual rather than group therapy approach is favoured due to the anticipated complexity of each individual's presenting problems. It will be ensured that the intervention can be delivered within the GP surgery, outpatient clinic or service user's home (for those who are unable to travel due to physical and/or mental health issues). The manualised intervention will be developed in close collaboration with the Project Service User Advisory Group, getting advice from them on how best to adapt the intervention for older people and the appropriateness of the materials.

Following development of the intervention, further individual qualitative interviews with the same set of 15 older people with GAD who completed the initial interviews will be conducted. Again, participants will be recruited from London and Oxfordshire to obtain a variety of service user perspectives. Interviews will examine: the acceptability and perceived value of the different components of the intervention; the practicalities of the intervention (e.g. number and frequency of sessions, settings, etc); and ways of optimising engagement (e.g. provision of mid-week telephone calls, peer mentors to provide support during therapy, etc). The feasibility of conducting ecological momentary assessment, a method of collecting real time data via smartphones, phone calls and emails that is more reliable and sensitive to change than paper-and-pencil measures will also be explored. Traditional paper-and-pencil measures typically enquire about mood over an extended period of time (e.g. the past week). Ecological momentary assessment enquires about mood in the present moment, and so, as well as being more appropriate for older people who may find it difficult to recollect how they have been feeling in the past week, may fit well with the core clinical processes addressed in ACT (e.g. mindful awareness of emotional experiences in the present moment). However, this assessment approach may not be feasible to complete if older people have limited access to smartphones or PCs, or if completion via phone calls in the absence of smartphone or PC access is perceived as burdensome. Two interested service users from qualitative interviews conducted at the beginning of Phase 1 will be invited to contribute to the analysis of these data. Following this, the intervention will be modified in collaboration with the Project Service User Advisory Group. Specifically, they will be invited to comment on qualitative interview data, and review the intervention and any proposed revisions before it is implemented in Phase 2.

<u>Phase 2: Evaluation of the intervention</u>

In Phase 2, the acceptability and feasibility of the intervention will be assessed within an open uncontrolled feasibility study. ACT will be delivered:

i) In an anticipated 16 1-hour sessions;

ii) With a phased ending such that sessions will be weekly for the first 14 weeks and every 2-3 weeks thereafter as some older people experience difficulties when therapy ends abruptly;

iii) Individually rather than in groups;

iv) Within the GP surgery, outpatient clinic or service user's own home;

v) By therapists attached to CMHTs for older people or IAPTs to increase the accessibility of the intervention. Although intervention delivery within IAPTs services would optimise access to treatment and NHS roll out, older people are under-represented in these services. The National Audit of Psychological Therapies found that only 6% of service users were aged 65 years or over, which is significantly lower than the expected rate of 13% (Royal College of Psychiatrists, 2013). A study in the East of England similarly reported that only 3.9% of referrals to IAPTs were aged 65+, again much lower than the expected access rate of 12.7% (Prina et al., 2014). This could mean that clinicians perceive IAPTs as not being suitable or accessible for older people, or that older people perceive these services as not being suitable or accessible for them.

ACT will be delivered by eight therapists: four in primary care (in IAPTs) and four in secondary care (in CMHTs for older people). Therapists will be Band 7 clinical psychologists, accredited CBT therapists or counselling psychologists, with a minimum of 1 year experience in delivering psychotherapy interventions. Ideally, therapists will be recruited who are already trained in ACT, but as therapists are not routinely trained in this approach in the NHS at present, this will be provided by members of the research team. Furthermore, although initial knowledge and/or experience in working with older people with treatment-resistant GAD will be desirable, additional training in delivering the intervention to this specific population will be provided. Therapists will be identified prior to the project starting (in the pre-orientation phase).

Therapists will initially attend a 4-day experientially-based training workshop on the use of ACT in people with anxiety and/or depression. This will be followed by six months of fortnightly group supervision via telephone by a Band 8 equivalent clinical psychologist or psychotherapist trained in ACT, with a minimum of five years' experience in delivering this therapy. It is envisaged that this training will occur in Phase 1 of the project while the manualised intervention is being developed. Following the development of the intervention, therapists will attend a 1-day experientially-based training workshop on the specific application of ACT to older people with treatment-resistant GAD. They will be given copies of the newly-developed client workbook and therapist manual to supplement training materials. Training will be delivered by members of the Project Development Group (two of whom are trained in ACT), and will include two interested service users identified from Phase 1 of the study. After completing training, therapists will deliver ACT for treatment-resistant GAD in older people within the feasibility study, under group supervision of the Band 8 equivalent clinical psychologist or psychotherapist (which will occur fortnightly via telephone). This degree of training is similar to that which was successfully employed in a training and implementation study of ACT for depression in the US (Walser et al., 2013), and is supported by evidence that ACT can be successfully delivered by novice therapists (Kohtala et al., 2015; Lappalainen et al., 2007; Wetherell et al., 2011).

All therapy sessions will be recorded using digital voice recorders in order to monitor adherence to the treatment manual, and will be reviewed in supervision sessions if a deviation from the manual is identified from the ACT checklist. Therapists will be asked to complete a checklist of ACT components, ACT techniques, and themes discussed in each session, together with any deviations from the manual, in order to monitor treatment adherence during supervision. This checklist will be adapted from that which is currently being used in the CanACT trial (Serfaty et al., 2014). In addition, 10% of sessions will be randomly selected and assessed for treatment fidelity by an independent ACT therapist using an adapted form of the ACT Treatment Integrity Coding Manual (Plumb et al., 2010). Random selection of sessions will be stratified according to therapist, phase of the intervention (early, middle or late), and phase of study recruitment (early, middle or late), as recommended in psychosocial interventions (Nezu et al., 2008).

Phase 3: Refinement of the intervention

In Phase 3, the intervention will be refined based on information gathered in Phase 2 from participants and therapists, in partnership with the Project Service User Advisory Group. They will be invited to comment on qualitative interview data from Phase 2, consider any proposed revisions, and review the final intervention.

8.2.2 Usual care

Phase 1: Clarifying usual care

In Phase 1, a brief, nationwide survey of clinicians' and service users' views of what constitutes usual care for treatment-resistant GAD in older people will be conducted in order to clarify the comparator for a future substantive trial. Although these data could be gathered solely from the open uncontrolled feasibility study using the Client Service Receipt Inventory (Beecham et al., 1992) in Phase 2, this information would potentially only be relevant to recruitment sites within London. It is likely that usual care for treatment-resistant GAD in older people will vary regionally (for example, with psychological therapies being easier to access in some areas e.g. cities compared to others e.g. rural settings), and so a brief nationwide survey will more accurately clarify what constitutes usual care in this population. Clinicians in primary and secondary care settings (including GPs, psychiatrists, clinical psychologists, community psychiatric nurses, occupational therapists, and social workers), together with service users, will be invited to participate in the survey. Clinicians will be identified through online forums associated with occupation-specific organisations such as the British Psychological Society, the Faculty of Old Age Psychiatry of the Royal College of Psychiatrists, the Primary Medical Performers List, General Medical Council, Clinical Advisors Network of the Royal College of General Practitioners, and Clinical Research Networks. Older service users with GAD will be identified through GP practices (recruited through Clinical Research Networks), Service User Research Forums, local community groups, anxiety-specific online forums (e.g. http://www.nomorepanic.co.uk/forum.php), and general mental health online forums (e.g. https://www.elefriends.org.uk). Service users with any form of GAD will be invited to complete the survey as opposed to treatment-resistant GAD as they may find it difficult to identify whether they have completed Steps 1-3 of the stepped care approach for GAD. Those with treatment-resistant GAD will be identified in post-hoc analyses so that what constitutes usual care in this specific group of respondents can be clarified. Paper- and online-based versions of the survey will be used to maximise data collection (and facilitate early promotion of the feasibility study). The paper-based version will be distributed via GP practices (e.g. questionnaires will be left in waiting rooms), local community groups, IAPTs, CMHTs for older people, and Service User Research Forums. If necessary, GP medical records within participating GP practices will also be electronically searched for service users with "GAD", "chronic anxiety" or "anxiety states" who have been seen in the past year. Once potentially eligible participants have been identified, nurses or GPs within participating GP practices will approach them and seek verbal consent for researchers to contact them. The online survey will be advertised through online forums noted above and will be conducted using Qualtrics, an online data collection software package. This is commonly used in academic clinical settings, and follows best practices for security as per Health Information Technology for Economic and Clinical Health Act requirements.

The brief survey will comprise a series of multiple-choice questions with free text boxes to enable provision of further information if desired. There will be two versions of the survey - one for clinicians and one for service users - as the content of questions and terminology will differ for these two groups of respondents. The clinician version will enquire about demographic information (e.g. age, profession, years since qualification, number of older people seen with treatment-resistant GAD on average per month, etc), what treatments are typically offered when an older service user has completed Steps 1-3 of the stepped care approach for

GAD, how often, and why treatments might not be offered, as well as perceptions of the helpfulness of these treatments rated on a 7-point Likert rating scale (from 1 = very unhelpful to 7 = very helpful). The service user version will include questions about demographic information (e.g. age, diagnosis, duration of GAD, etc), what treatments have been offered previously or currently, whether they were taken up, and perceptions of the helpfulness of these treatments on a 7-point Likert rating scale (from 1 = very unhelpful to 7 = very helpful). It will also include a brief screening tool that is already routinely used in Improving Access to Psychological Therapies services and GP surgeries, the Generalized Anxiety Disorder-7 (Spitzer et al., 2006), to indicate those who are experiencing current difficulties with GAD. The survey will be brief to maximise completion rates, and it is envisaged that it will take 5-10 minutes to complete.

8.3 Subsequent assessments and procedures

This section describes all proposed outcome measures and assessments in Phase 2. Data collection will be conducted face-to-face (or via telephone at 20 weeks if face-to-face data collection is problematic).

Primary outcome measures

The co-primary outcome measures will be:

i) Acceptability:

a) Participants attending >=60% sessions;

b) 'Satisfactory' ratings of therapy using the Satisfaction with Therapy and Therapist Scale-Revised (Oei et al., 2008): A 12-item self-report measure of satisfaction with therapy and satisfaction with the therapist, rated on a 5-point scale from 1 (strongly disagree) to 5 (strongly agree). There is no set definition of what constitutes "satisfactory" and so we will define this as a total score of 21 or more on the Satisfaction with Therapy subscale.

ii) Feasibility:

a) Recruitment of >= 80% of the target sample size in a 10 month recruitment period;

b) Retention rate of >=60%.

Secondary outcome measures

The secondary outcome measures will be:

i) Acceptability:

a) Failures to recruit due to lack of acceptability of the intervention;

b) Participants dropped out due to lack of acceptability of the intervention;

c) Credibility/Expectancy Questionnaire (Devilly et al., 2000): It is important to evaluate treatment credibility/expectancy when developing a new intervention as this can have a significant impact on uptake and dropout rates. The Credibility/Expectancy Questionnaire is a 6-item self-report measure that assesses the credibility of the rationale for therapy and treatment expectancy, which will be adapted for GAD and measured immediately after the first therapy session. Four items are rated on a 9-point scale from 1 to 9 (lower scores are worse) and 2 items are scored on an 11-point scale from 0 to 100%. As the measure includes items rated on two scales, the items will be standardised and summed to form separate composite scores for credibility and expectancy.

ii) Feasibility:

a) Eligible referrals overall and in each referral subgroup (self-referral, GPs, GP list searches, Improving Access to Psychological Therapies services, and Community Mental Health Teams);

b) Eligible participants recruited;

c) Failures to recruit for reasons other than dissatisfaction with therapy (together with reasons for this);

d) Participants dropped out for reasons other than dissatisfaction with therapy (together with reasons for this);

e) ACT Treatment Integrity Coding Manual (Plumb et al., 2010): A coding system that has been developed to assess treatment integrity in ACT interventions, which has been used in previous randomised controlled trials of ACT (Twohig et al., 2010). In this coding system, the frequency and depth of coverage of major components of ACT (defusion, willingness/acceptance, creative hopelessness/workability, values and goals, committed action, general assessment of goals for treatment, symptoms and general functioning), together with overall adherence and overall therapist competence, are rated on a five-point scale from 1 (not at all) to 5 (extensively). Coding will be completed by an independent ACT therapist;

f) Adherence Checklist: A checklist of ACT components, ACT techniques, and themes discussed in each session, together with any deviations from the manual, which will be adapted from that which is currently being used in the CanACT trial (Serfaty et al., 2014). The outcome will be deviations from the manual.

iii) Patient-reported outcome measures at 0 and 20 weeks:

a) Geriatric Anxiety Inventory (Pachana et al., 2007): A 20-item "agree/disagree" self-report measure of anxiety developed specifically for older people so that it minimises somatic symptoms as these frequently overlap with physical health conditions commonly found in older people;

b) Penn State Worry Questionnaire (Meyer et al., 1990): A 16-item self-report measure of worry severity widely used in GAD, rated on a 5-point scale from 0 (not at all typical of me) to 5 (very typical of me);

c) Geriatric Depression Scale-15 (Yesavage et al., 1983): A 15-item "yes/no" self-report measure of depression developed specifically for use with older people for reasons noted above, necessary as GAD is most frequently comorbid with depression;

d) EQ-5D-5L including the VAS (EuroQol Group, 1990; Herdman et al., 2011): A 5-item self-report measure of health-related quality of life, used to calculate utility scores for quality-adjusted life years, rated on a 5-point scale from no problems to extreme problems;
e) A short modified version of the Client Service Receipt Inventory (Beecham et al., 1992; Serfaty et al., 2009): A measure of service utilization, used to calculate quality-adjusted life years. Where consent is provided, data will also be extracted from GP medical records on GP/nurse consultations, prescribing and referrals in the 20 weeks before baseline and during receipt of ACT;
f) Acceptance and Action Questionnaire-II (Bond et al., 2011): A 7-item process measure of experiential avoidance or psychological inflexibility commonly used in ACT and currently being used in the CanACT trial (Serfaty et al., 2014).

Qualitative interviews
Individual qualitative interviews will be conducted with an estimated 15 participants, or until saturation is reached, after completing therapy in Phase 2 to further examine the acceptability and feasibility of the intervention. The perceived benefits and limitations of the intervention will be explored, together with any recommendations for revising the manual. Purposive sampling will be conducted on the basis of sex, socio-economic status, ethnicity, recruitment source and session attendance to explore a range of perspectives. All therapists will be interviewed to examine how the intervention was delivered in practice (e.g. treatment fidelity, ease of delivering ACT for treatment-resistant GAD in older people, difficulty of skills for participants to learn, etc).

Monitoring measures:
As a drug stabilisation period will not be included in the feasibility study, the name, dose and frequency of all psychotropic medication prescribed, and any changes to this, will be recorded during the course of the study. This information will be extracted from GP medical records, with participants' consent. This will then be included as a covariate in statistical analyses. Participants will be asked to refrain from engaging in other forms of psychotherapy during the delivery of the intervention as engaging in two types of psychotherapy concurrently may lead to conflicts in therapeutic approaches and goals. Other psychological or psychosocial interventions that participants engage in during the course of the study will be recorded, along with any interventions that participants are referred for after receiving the intervention. Evidence of any adverse effects from the intervention will also be monitored and recorded throughout the feasibility study.

8.4 Discontinuation/withdrawal of participants
In consenting to participate in the study, participants are consenting to intervention, assessments, follow-up and data collection. A participant may be withdrawn from the study whenever continued participation is no longer in the participant's best interests, but the reasons for doing so must be recorded (whenever possible). Reasons for discontinuing the study may include:

- active suicidal ideation with intent and plans;
- illness that may exclude the possibility of engagement in the intervention;
- a person withdrawing consent or losing the capacity to consent to participate in the study.

The decision to withdraw a participant from treatment will be recorded in the Case Report Form (CRF) and Investigator Site Files. If a participant explicitly states they do not wish to contribute further data to the study their decision must be respected and recorded in the CRF.

8.5 Definition of end of trial
The expected duration of the study is 20 months from recruitment of the first participant. The end of the study is the date of the last follow up visit of the last participant.

9 Recording and reporting of adverse events
9.1 Unblinding
Not applicable as the study is an open uncontrolled feasibility study.

9.2 Notification of reportable protocol violations
A reportable protocol violation is a breach which is likely to effect to a significant degree:
(a) the safety or physical or mental integrity of the participants of the study; or
(b) the scientific value of the study.
The sponsor will be notified immediately of any case where the above definition applies during the study conduct phase. The Chief Investigator or designated individual will notify the sponsor of any protocol violation.

9.3 Trust incidents and near misses
An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.
b. It is contrary to specified or expected standard of patient care or service.
c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d. It puts the Trust in an adverse position with potential loss of reputation.
e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses will be reported to the Trust through DATIX as soon as the individual becomes aware of them. A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

10 Data management

10.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998. The CRFs will not bear the participant's name or other personal identifiable data. The participant's initials, date of birth and study identification number, will be used for identification and this will be clearly explained to the patient in the Patient information sheet. Patient consent for this will be sought. All participant information will be stored in accordance with the UK Data protection Act 1998 guidance, with all personally identifiable information, stored in locked cabinets and stored separately from study data which will be pseudonymised and saved on password-protected computers at UCL. Each participant will be assigned an identification code, which will be used in all data storage, and will not contain any names or other personally identifiable information. After completion of the study all personal details will be deleted.

Participants will be assured that confidentiality will be kept unless there is evidence of risk of harm to self or others. This will be specified in the information sheet. If the screening assessment reveals undiagnosed disorders such as cognitive impairment suggestive of a neurodegenerative condition (identified from the Standardised Mini-Mental State Examination), or other undiagnosed psychiatric conditions (identified from the MINI International Neuropsychiatric Interview or Structured Clinical Interview for DSM-IV Axis II Disorders), then the participant's GP will be informed with their consent (or without their consent if there are concerns about risk of harm to self). Participants' GPs will also be informed of their participation in the study, with their consent.

10.2 Data collection tools and source document identification

Data will be collected from sites on study-specific CRFs or data collection tools such as electronic CRFs. Source data contained in source documents will be accurately transcribed onto the CRFs. Methods to maximise completeness of data will be applied when necessary. The Chief Investigator will have the primary responsibility of ensuring all data entered in the CRFs are accurate. A delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database (Chief Investigator, Trial statistician, Research Assistant).

10.3 Completing Case Report Forms

All CRFs will be completed and signed by staff that are listed on the site staff delegation log and authorised by the Chief Investigator/Principal Investigator to perform this duty. The Chief Investigator will be responsible for the accuracy of all data reported in the CRF. In line with UCL's Data Protection Policy, trial documentation and anonymous data will be securely kept for a period of 10 years following completion of the study. All data from all sites taking part in this project will be kept and monitored at UCL. The Chief Investigator and or a designated individual will be responsible for any data queries.

10.4 Data handling

All data will be collected in accordance with the patient consent form, patient information sheet and section 8.4 of this protocol. UCL, as the study sponsor will act as the data controller for the study. All data will be handled in accordance with the UK Data Protection Act (1998). All data will be pseudo-anonymised using unique identification numbers and stored without contact details (names or addresses). Associations between participants' contact details and identification numbers will be stored in a separate encrypted electronic password-protected database. Access to this document will be restricted to the Chief Investigator and the research assistant. All data will be held on a secure database on a password-protected computer, and access to it will be restricted to the research team. Study consent forms will be kept in a locked cabinet at UCL for 10 years. Access to data will be restricted to the research team. Audio files of qualitative interviews and therapy sessions recorded on digital voice recorders will be uploaded to a secure server using a system called Data Safe Haven, which satisfies the highest level security requirements of NHS trusts. Treatment integrity ratings will be completed by an independent ACT therapist who will review audio files stored on the secure server using a UCL password protected computer. Transcriptions of qualitative interviews will be completed as soon as possible after collection and anonymised. Data will not be transferred to any party not identified in this protocol and will not to be processed and/or transferred other than in accordance with the patients' consent.

Quality control

Compliance to Good Clinical Practice (GCP) is now a requirement for all clinical trials. Accurate records will be kept, in line with the research protocol, in relation to recruitment, randomisation and data collection. Data will be collected and managed in a systematic way, and researchers will be trained, supervised and supported. Compliance to GCP, and quality control will be monitored in the beginning monthly and every three months subsequently. The Chief Investigator will ensure that all records are

maintained and participant confidentiality is assured. Quality control to a sample of data will be performed during the first weeks of data collection. Investigator Site Files and a Master file will also be kept that will source all documents of the study.

11 Statistical considerations

11.1 Primary outcome(s)

The indicators of success will be:

i) Acceptability:
a) Participants attending >=60% sessions;
b) 'Satisfactory' ratings of therapy, defined as a total score of 21 or more on the Satisfaction with Therapy and Therapist Scale-Revised (Oei et al., 2008).

ii) Feasibility:
a) Recruitment of >= 80% of the target sample size in a 10 month recruitment period;
b) Retention rate of >=60% as measured by attendance at the final follow-up assessment.

Three out of four criteria will need to be met in order for success to be demonstrated.

11.2 Secondary outcome(s)

i) Acceptability:
a) Failures to recruit due to lack of acceptability of the intervention;
b) Participants dropped out due to lack of acceptability of the intervention;
c) Credibility/Expectancy Questionnaire (Devilly et al., 2000) after the 1st session of the intervention.

ii) Feasibility:
a) Eligible referrals overall and in each referral subgroup (self-referral, GPs, GP list searches, Improving Access to Psychological Therapies services, and Community Mental Health Teams);
b) Eligible participants recruited;
c) Failures to recruit for reasons other than dissatisfaction with therapy (together with reasons for this);
d) Participants dropped out for reasons other than dissatisfaction with therapy (together with reasons for this);
e) Scores on the ACT Treatment Integrity Coding Manual (Plumb et al., 2010);
f) Deviations from the manual using the Adherence Checklist.

iii) Patient-reported outcome measures at 0 and 20 weeks:
a) Geriatric Anxiety Inventory (Pachana et al., 2007);
b) Penn State Worry Questionnaire (Meyer et al., 1990);
c) Geriatric Depression Scale-15 (Yesavage et al., 1983);
d) EQ-5D-5L including the VAS (EuroQol Group, 1990; Herdman et al., 2011);
e) A short modified version of the Client Service Receipt Inventory (Beecham et al., 1992; Serfaty et al., 2009);
f) Acceptance and Action Questionnaire-II (Bond et al., 2011).

11.3 Sample size calculation

The recruitment figure in Phase 1 is based on a sample size of 15 participants, consistent with the sample size recommended for qualitative interviews (Guest et al., 2006). The recruitment figure in Phase 2 is based on a sample size of 40 participants. A sample size of 35 is recommended in feasibility studies in order to provide sufficient data and precision of means and variances (Teare et al., 2014). Forty participants allows for a 12.5% loss to follow-up based on a preliminary study of ACT in older people with GAD (Wetherell et al., 2011a). With respect to session attendance, making the conservative assumption that 80% of participants in the feasibility study will attend 60% or more of sessions, a sample size of 35 (after loss to follow up) will give a 95% confidence interval of 0.63 to 0.92, indicating that we could be 95% certain that at least 63% of the target population will attend 60% or more of sessions. Although 100% attendance of ACT sessions was reported in 100% of older people with any form of GAD (i.e. not specifically treatment-resistant GAD; Wetherell et al., 2011a) and 78% of older people with depression (Karlin et al., 2013), a conservative estimate has been chosen given the target population. With respect to recruitment, making a conservative estimate that 60 participants will be eligible to participate in the feasibility study but only 40 will consent to participate, a sample size of 40 will give a 95% confidence interval of 0.53 to 0.78.

11.4 Planned recruitment rate

In Phase 1, it is estimated that approximately 50 older people with treatment-resistant GAD will need to be identified and approached in order for 15 people to agree to participate in the study. In Phase 2, it is estimated that approximately 131 older people with treatment-resistant GAD will need to be identified and approached in order for 40 people to agree to participate in the study. These rates allow for 35% to decline participation, and 53% of those who are interested in participating to be assessed as ineligible based on rates reported in a previous study of CBT for GAD in older people (Stanley et al., 2009). In order to meet the target recruitment rate of 15 participants within 4 months in Phase 1 and 40 participants within 10 months in Phase 2, the identification rate will need to be approximately 13 potential participants per month, of whom it is estimated that 4 will be suitable

and will agree to participate per month. The recruitment period is 4 months in Phase 1 and 10 months in Phase 2. Full details of timeline appear in Appendix 2.

An ICD-10 diagnosis of GAD was recorded in 96 service users aged 65+ within secondary and tertiary care services during 01.04.15-11.01.16 in South London and Maudsley NHS Trust alone. Therefore, the referral rate appears feasible given that: i) GAD is the most common anxiety disorder in older people; ii) referrals will come from many sources in community, primary and secondary care settings; and iii) there are limited exclusion criteria. While these appear to be reasonable assumptions, if uptake is slower than expected then recruitment sites will be expanded to other regions in London.

11.5 Statistical analysis

11.5.1 Summary of baseline data and flow of participants

Essential socio-demographic and clinical data will be recorded at screening and baseline as follows:
i) Age, sex, ethnicity, marital status, years of education, highest level of educational qualification, current occupation, and highest level of occupational attainment;
ii) Psychiatric diagnoses using the MINI International Neuropsychiatric Interview (Sheehan et al., 1998) and the Structured Clinical Interview for DSM-IV Axis II Disorders (First et al., 1995, 1997);
iii) Previous and current treatment for GAD, ongoing medication use including prescribed or illicit substances (dose and frequency) and length of current episode;
iv) GAD using the Generalized Anxiety Disorder-7 (Spitzer et al., 2006);
v) Global cognition using the Standardised Mini-Mental State Examination (Molloy et al., 1991);
vi) Suicidal ideation, intent and plans;
vii) Physical illness and disability using the Cumulative Illness Rating Scale-Geriatrics (Miller et al., 1992).

The feasibility study will produce a consort flow diagram in order to inform a future substantive trial.

11.5.2 Primary outcome analysis

In line with current recommendations of GCP in the analysis of feasibility studies, quantitative analyses will be descriptive. Binary and other categorical measures will be summarised using frequencies and percentages, and continuous measures using means and standard deviations (or medians and interquartile ranges for very skewed distributions). The precision of estimates will be assessed using 95% confidence intervals.

11.5.3 Secondary outcome analysis

Several clinical outcome measures will be evaluated for suitability for a future substantive trial. Binary and other categorical measures will be summarised using frequencies and percentages, and continuous measures using means and standard deviations (or medians and interquartile ranges for very skewed distributions). The precision of estimates will be assessed using 95% confidence intervals. Change in patient-reported outcome measures between 0 and 20 weeks will be estimated using multilevel linear or logistic regression models with a random effect of person to account for the repeated measures on individuals over time. Potential cluster effects by site and therapist will be accounted for using appropriate statistical methods. Unadjusted and adjusted results will be presented, with therapist, psychotropic medication, Standardised Mini-Mental State Examination score, number of comorbid mental health disorders and symptom severity at baseline as covariates in adjusted analyses. Cognitive function, psychiatric comorbidity and symptom severity are selected as covariates as they have been associated with poor treatment response in older people with GAD (Caudle et al., 2007; Stanley et al., 2009; Wetherell et al., 2005).

11.5.4 Sensitivity and other planned analyses

Some missing data is anticipated at 20 week follow-up. The number of missing values for each of the outcome measures will be summarised and reported. Multilevel models for longitudinal data account for missing data under the missing at random assumption (i.e. that missingness is conditional on other observed measures included in the analysis). Power analyses will be conducted to calculate the sample size necessary to detect an effect of the intervention in a future substantive trial. A more detailed statistical analysis plan will be produced as a separate document by the Project Statistician. Formal records will be kept of the statistical analysis plan and how it can inform a future substantive trial.

11.5.5 Qualitative data

Qualitative data will be transcribed verbatim and analysed iteratively using thematic analysis (Braun et al., 2006). Phase 1 will adopt an inductive approach, using constant comparison method (Glaser, 1978) to delineate themes and sub-themes relating to participants' experiences and attitudes towards psychotherapy. Multiple coding will be conducted on three transcripts to allow researchers to identify and discuss any alternative interpretations. Data from the second wave of interviews in Phase 1 and interviews in Phase 2 will be subject to a focussed thematic analysis. Three members of the research team will independently code initial data before constructing an analytical framework around the perceived value, acceptability and feasibility of the intervention. The analytical framework will be applied to the remaining transcripts, with themes and subthemes refined as necessary. Two interested service users from the first wave of qualitative interviews conducted in Phase 1 will be invited to be involved in coding the second wave of qualitative interviews in Phase 1. Interviews will be coded anonymously to maintain confidentiality. Ideas about themes and their relationships will be recorded in theoretical memos and discussed among the Project

Service User Advisory Group/Project Management Group. The computer programme QSR N-VIVO will be used to process the transcripts, enabling us to code and retrieve a large volume of narrative data.

11.5.6 Economic evaluation

The overall mean cost of service use per participant will be calculated by calculating the mean cost of: i) health and social care resource use during the 20 weeks of the feasibility study using a short modified version of the Client Service Receipt Inventory (Beecham et al., 1992; Serfaty et al., 2009); ii) health and social care resource use for the preceding 20 weeks so that service use at baseline can be adjusted for; and iii) delivering ACT based on the number of sessions attended per participant, session duration, therapists' pay grade, training, supervision and overhead costs. Nationally published costs will be used to calculate the total cost of resource use per participant. The overall mean cost per participant and confidence intervals will then be calculated, adjusting for baseline service use.

12 Record keeping and archiving

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that he/she will archive the study master file at UCL for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. At the end of the trial, all essential documentation will be archived securely by the Chief Investigator for a minimum of 10 years from the declaration of end of trial. Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether each site complied with all applicable regulatory requirements. The sponsor will notify the coordinating site (where all data will be stored) when trial documentation can be archived. All archived documents will continue to be available for inspection by appropriate authorities upon request.

13 Oversight Committees

Study Steering Committee

A Study Steering Committee (SSC) has been set-up and will include an independent Chair, an independent statistician, an independent clinician, and one non-independent PPI collaborator. The Committee will meet once a year to review progress and address any issues as necessary. Representatives of the sponsor and research network will also be invited to attend meetings. The SSC will be combined with the Independent Data Monitoring Committee (IDMC), given that this is a small feasibility study. The role of the SSC is to provide overall supervision of the trial, recommendations in relation to data monitoring, and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. It will discuss issues related to data collection, ethical issues and other incidents. The SSC will also act on behalf of the funder and Sponsor, and will provide independent advice on data and safety aspects of the trial. Since the SSC is acting as the IDMC, it can recommend premature closure of the trial.

Research governance and conduct of the study

The study will be conducted in line with the Helsinki Declaration. UCL is the nominated sponsor.

13.1 Project Development Group and Project Management Group

The Project Development Group will include the Chief Investigator, Co-Investigators, PPI collaborator and study staff (Research Assistant). This group will meet at the beginning of the project in person and by teleconference to outline the development of the intervention, the tasks involved, and target deadlines in Phase 1. The group will then meet weekly thereafter to ensure continued progress and attainment of milestones. Once the intervention has been developed, a Project Management Group (PMG) comprising the Chief Investigator, Co-Investigators, PPI collaborator, an interested member of the Project Service User Advisory Group and study staff (Research Assistant) will meet in person and by teleconference every 3 months throughout the remainder of the project. This group will be responsible for overseeing the study and will set target deadlines for Phases 2 and 3, monitor the conduct and progress of the project, and trouble shoot any issues that arise. It will also ensure adherence to Mental Capacity and Data Protection Acts, ethical guidelines, Information Governance procedures, and the British Psychological Society's Code of Conduct for Research. The PMG will review recruitment figures, incidents and substantial amendments to the protocol prior to submission to the Research Ethics Committee (REC). All Co-Investigators will be kept informed of substantial amendments by the Chief Investigator or other designated individual. The group will send updates to the SSC.

Expertise of CIs and collaborators

The multi-professional team comprises experts in the fields of mental health of older people, anxiety disorders, and the development and use of manual-based complex psychological interventions: Dr Rebecca Gould (RG, Senior Research Associate and Honorary Clinical Psychologist, Department of Psychiatry, UCL), Professor Robert Howard (RH, Professor of Old Age Psychiatry, Division of Psychiatry, UCL), Dr Marc Serfaty (MS, Reader in Psychiatry, Division of Psychiatry, UCL), Professor Gill Livingston (GL, Professor of Psychiatry of Older People, Division of Psychiatry, UCL), Dr Philip Wilkinson (PW, Honorary Senior Clinical Lecturer and Consultant Psychiatrist, Department of Psychiatry, University of Oxford), Dr Kate Walters (KW, GP, senior clinical lecturer and Director of the Centre for Ageing & Population Studies, UCL), Ms Rebecca Jones (RJ, Senior Research Associate, Division of Psychiatry, UCL), and Dr Vanessa Lawrence (VL, Lecturer in Qualitative Social Sciences, Health Services and Population Research, King's College London). In addition, the study's collaborators include: Dr Julie Loebach Wetherell (JLW, Professor In Residence, Department of Psychiatry, University of California, San Diego), Dr Viviana Wuthrich (VW, Senior Lecturer and Clinical Psychologist, Department of Psychology, Macquarie University), Dr Janet Wingrove (JW,

consultant clinical psychologist and Clinical Director of the Improving Access to Psychological Therapies service in Southwark), Mr Steve Boddington (SB, consultant clinical psychologist and Head of Psychology and Psychological Therapy for older people within South London and Maudsley NHS Trust), and DH, an older service user with personal experience of GAD.

The team has extensive experience of successfully developing and evaluating psychotherapy manuals for anxiety and depression in older people within clinical trials, including ACT for GAD (JLW), CBT for GAD (JLW), CBT for depression (MS, PW), and transdiagnostic CBT for comorbid anxiety and depression (VW, RG). In addition, GL has significant expertise in developing and evaluating complex non-pharmacological interventions for people with dementia and their carers (START and MARQUE projects). MS has clinical expertise in delivering ACT to older people with advanced cancer, and is currently Chief Investigator of a study of ACT in palliative care (CanACT), as well as being a co-applicant in a study of sertraline vs. CBT for GAD (ToSCA). RG has clinical training in delivering mindfulness- and acceptance-based interventions including ACT to older people with anxiety and depression. RJ and VL will provide expertise in collecting and analysing quantitative and qualitative data, respectively. KW has significant experience of conducting clinical research in primary care settings, including developing complex interventions for frail older people (e.g. http://www.nets.nihr.ac.uk/projects/hta/1219210) and recruiting older people and people with mental health difficulties from primary care. RG will be mentored by RH and MS, who have extensive experience of successfully conducting clinical trials and mentoring junior researchers. Numerous members of the team have previous experience of successfully working together (e.g. RG & RH; PW & RH; GL& RH; GL, KW & RJ; JLW & VW), and of leading NIHR-funded studies (GL, KW, MS, RH). The team will work with KW, JW and SB to ensure that the intervention is appropriate for older people with treatment-resistant GAD who have failed to respond to interventions delivered within primary care, and is appropriate for delivery within primary or secondary care services. The team will work with DH to ensure the intervention is relevant, practical and appropriate for older people with treatment-resistant GAD.

14 Ethical requirements and patient and public involvement

14.1 Ethical requirements

Ethical and research governance approvals through the Health Research Authority will be obtained prior to the study commencing. The sponsor will ensure that the study protocol, Participant Information Sheet, ICFs, GP letter and submitted supporting documents have been approved by the appropriate REC, prior to any participant recruitment. The protocol, all other supporting documents including and agreed amendments, will be documented and submitted for ethical and regulatory approval in line with Governance Arrangements for NHS Research Ethics and Quality Assurance guidelines. Ethical concerns arising from the study will be reviewed by the SSC and IDMEC. All researchers will receive training in line with the GCP guidelines. The study has been registered as a clinical trial and has been allocated an International Standard Randomised Controlled Trial ID Number (ISRCTN12268776). As the intervention is psychological, the study is not covered by the Medicines for Human Use (Clinical Trials) Regulations 2004.

Amendments will not be implemented prior to receipt of the required approvals. Before any NHS site may be opened to recruit participants, the Chief Investigator or designee must receive confirmation of capability and capacity in writing from the Trust Research & Development (R&D). It is the responsibility of the Chief Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approvals, including NHS Permission (where required) at the site. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual participants (see section 9.6 for reporting urgent safety measures). An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The Chief Investigator will prepare the annual progress report. Within 90 days after the end of the trial, the Chief Investigator/Sponsor will ensure that the main REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The Chief Investigator will supply the Sponsor with a summary report of the trial, which will then be submitted to the REC within 1 year after the end of the trial.

14.2 Patient and public involvement

The proposal was devised with input from older members of the Service User Clinical Academic Group and the Service User Advisory Group who gave specific advice on the design of the study, patient and public involvement, and lay communication. The feasibility of the intervention has been discussed with staff from CMHTs and IAPTs. Service user involvement will occur in a number of ways in order to provide partnership and enhance the relevance, appropriateness and practicality of the intervention:

i) Project Service User Advisory Group: Five interested service users from qualitative interviews conducted in Phase 1 will be invited to be members of the Project Service User Advisory Group. The manualised intervention will be developed and refined in close collaboration with them, getting advice from them on how best to adapt the intervention for older people and the appropriateness of the materials. They will also advise on research management, study literature preparation and dissemination of the findings (in conjunction with members of the UCL Service User Research Forum and King's College London Service User Advisory Group);

ii) Project Management Group: An interested member of the Project Service User Advisory Group will be invited to be part of the Project Management Group;

iii) Service User coders: Two interested service users from the first wave of qualitative interviews conducted in Phase 1 will be invited to be involved in analysing the second wave of qualitative interviews in Phase 1, dependent on their level of expertise and

interest. This opportunity will range from reading transcripts and discussing themes/coding frameworks to participating in coding data. Training and support in all of these roles will be provided, where necessary;
iv) Service User involvement in training: Two interested service users from the Project Service User Advisory Group or qualitative interviews will be invited to participate in training therapists in how to apply ACT skills to older people with treatment-resistant GAD in Phase 2 (with training and support from the Chief Investigator);
v) Service User involvement in dissemination: An interested service user from the Project Service User Advisory Group will be invited to participate in presentations of the findings to Service User groups in Phase 3 (with training and support from the Chief Investigator).

15 Monitoring

The sponsor will determine the appropriate level and nature of monitoring required for the study. Standard Operating Procedures of the Sponsor will be followed. Risk will be assessed on an ongoing basis and adjustments will be made accordingly. The degree of monitoring will be proportionate to the risks associated with the study. A study specific oversight and monitoring plan will be established prior to the commencement of the study. The study will be monitored in accordance with the agreed plan. GCP will be followed by monitoring participants for suicide risk throughout the duration of the study and in all contacts with participants. Participants will remain under the care of their GP/consultant psychiatrist/care coordinator for the duration of the open uncontrolled feasibility study. Risk of harm to self or others will be monitored throughout the study. If suicidal ideation without intent is expressed at any point) then the participant's GP/consultant psychiatrist/care coordinator will be contacted and the participant will continue to be monitored weekly. If suicidal ideation with active intent is expressed at any point then the participant's GP/consultant psychiatrist/care coordinator will be contacted and the participant will be referred for urgent psychiatric assessment. The decision as to whether the participant should be withdrawn from the study will depend on the outcome of this assessment, and in full discussion with the participant and clinical team. Incidents will be recorded and reported to the IDMEC, SSC, sponsor of the trial and ethics committee, and if serious or life threatening will be reported within 15 days of knowledge.

16 Finance

This project is funded by the NIHR HTA. There are no financial interests for the Chief Investigator, Co-Investigators, collaborators or SSC members.

17 Insurance

UCL holds insurance against claims from participants for injury caused by their participation in the study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the study. UCL does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this study without the need to prove negligence on the part of UCL or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this trial shall provide negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to UCL, upon request.

18 Dissemination and publication policy

18.1 Dissemination

Dissemination to the mental health and primary care academic and clinical community, service users and the broader public will occur through:

i) Peer-reviewed, international academic journals such as the Journal of the American Geriatrics Society, the International Journal of Geriatric Psychiatry, and the Journal of Consulting and Clinical Psychology. Findings will be reported in accordance with reporting guidelines for quantitative cohort studies (STROBE; von Elm et al., 2007) and qualitative research (COREQ; Tong et al., 2007), as well as guidelines relevant to non-pharmacological treatment interventions (e.g. CONSORT for non-pharmacological treatment interventions; Boutron et al., 2008);
ii) National and international academic conferences (e.g. British Association for Behavioural & Cognitive Psychotherapies, World Congress of Behavioural and Cognitive Therapies);
iii) Local clinical conferences and meetings;
iv) Talks to local Service User groups, Primary Care Research Network, MIND and other organisations following guidance from the Project Service User Advisory Group, and including an interested service user from this group;
v) University media releases, twitter feeds and the University website.

18.2 Publication policy

A publication dissemination policy will be developed as part of this project. Publications arising directly or indirectly from the FACTOID project will adhere to the UCL and BMJ (2009) guidelines on authorship and contributorship. These state that 'authorship credit should reflect substantial contribution to:

- conception and design, or analysis and interpretation of data;
- drafting the article or revising it critically for important intellectual content;
- and final approval of the version to be published.

All these conditions must be met. All proposed publications will be discussed with and reviewed by the Sponsor prior to publishing, other than those presented at scientific forums/meetings.

19 Intellectual property

All background intellectual property rights (including licences) and know-how used in connection with the study shall remain the property of the party introducing the same and the exercise of such rights for purposes of the study shall not infringe any third party's rights.

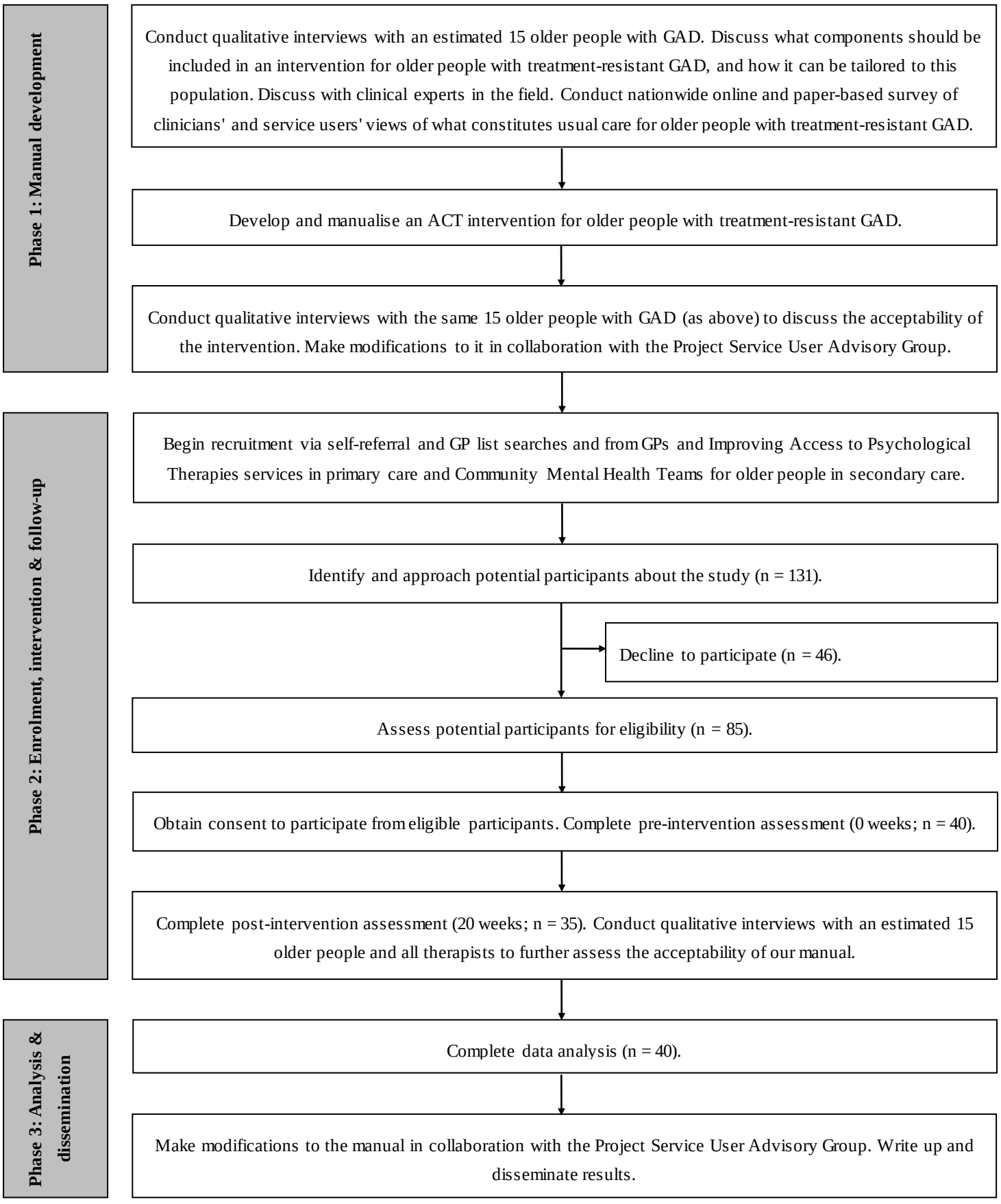
All intellectual property rights and know-how in the protocol and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to UCLH. Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to UCL and to disclose all such know-how to UCL. Each participating site agrees to, at the request and expense of UCL execute all such documents and do all acts necessary to fully vest the IPR in UCL.

Nothing in this section (Section 19) shall be construed so as to prevent or hinder the participating site from using know-how gained during the performance of the study in the furtherance of its normal activities of providing or commissioning clinical services, teaching and research to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of UCL. This does not permit the disclosure of any of the results of the study, all of which remain confidential.

20 Declaration of interests

None declared.

Appendix 1 – Flowchart of phases in the FACTOID study.



Appendix 2 – Project timetable and milestones

Date	Activity	Milestone(s)
Months -6-0: Nov 2016-Apr 2017	Pre-orientation	Apply for ethical and research governance approvals. Place advert for research assistant with date of interview. Devise 4-day training workshop. Identify therapists.
Months 1-3: May-Jul 2017	Orientation & Phase 1: Develop manual	Interview and appoint research assistant. Purchase equipment. Develop procedures and policies for the conduct of the study. Set up Project Development Group, Project Management Group and Study Steering Committee. Conduct first wave of qualitative interviews with service users. Discuss manual development with experts. Conduct 4-day training workshop on ACT with therapists. Set up online- and paper-based nationwide survey of what constitutes usual care for treatment-resistant GAD in older people.
Months 4-6: Aug-Oct 2017	Phase 1: Develop manual	Analyse qualitative data. Develop manual. Conduct second wave of qualitative interviews with service users. Make modifications to the intervention based on interview data, in partnership with the Project Service User Advisory Group. Devise 1-day training workshop on applying ACT to older people with treatment-resistant GAD.
Months 7-9: Nov 2017-Jan 2018	Phase 2: Feasibility study	Conduct 1-day training workshop on applying ACT to older people with treatment-resistant GAD with therapists. Recruit participants at a rate of 4 participants per month. Deliver ACT.
Months 10-20: Feb-Dec 2018	Phase 2: Feasibility study	Recruit participants (finish by end of Aug 2018). Deliver ACT intervention (finish by end of Dec 2018). Collect outcome measures and conduct qualitative interviews with participants and therapists.
Month 21: Jan 2019	Phase 3: Data analysis	Clean and analyse quantitative and qualitative data. Rate ACT tapes.
Months 22-24: Feb-Apr 2019	Phase 3: Write up & revise manual	Prepare final report. Write draft of paper. Make final modifications to the intervention with the Project Service User Advisory Group. Disseminate findings. Prepare application for funding of a substantive trial.

Months	**-6-0**	**1-3**	**4-6**	**7-9**	**10-12**	**13-15**	**16-18**	**19-21**	**22-24**
Dates	Nov 2016-Apr 2017	May-Jul 2017	Aug-Oct 2017	Nov 2017-Jan 2018	Feb-Apr 2018	May-Jul 2018	Aug-Oct 2018	Nov 2018-Jan 2019	Feb-Apr 2019
Pre-orientation									
Orientation									
Develop intervention									
Conduct survey									
Recruitment									
Deliver ACT									
Data analysis									
Write up & disseminate results									
Revise intervention									

Appendix 3 – References

Alonso-Fernandez, M.A., Lopez, A., Losada, A., et al. 2013. Acceptance and commitment therapy and selective optimization with compensation for older people with chronic pain: A pilot study. *Behavioral Psychology*, 21(1), pp.59–79.

Alonso-Fernández, M., López-López, A., Losada A., et al. 2015. Acceptance and Commitment Therapy and selective optimization with compensation for institutionalized older people with chronic pain. *Pain Medicine*. Epub ahead of print.

Avdagica, E., Morrissey, S.A., & Boschen, M.J. 2014. A randomised controlled trial of Acceptance and Commitment Therapy and Cognitive-Behaviour Therapy for generalised anxiety disorder. *Behaviour Change*, 31(02), pp.110-130.

Baltes, P.B., & Baltes, M.M. 1990. Psychological perspectives on successful aging: the model of selective optimization with compensation. In: P.B. Baltes, & M.M. Baltes, eds. *Successful Aging: Perspectives from the Behavioral Sciences*. Cambridge, United Kingdom: Cambridge University Press. pp.1–34.

Barton, S., Karner, C., Salih, F., et al. 2014. Clinical effectiveness of interventions for treatment-resistant anxiety in older people: a systematic review. *Health Technology Assessment*, 18(50), pp.1-59.

Beecham, J., & Knapp, M. 1992. Costing psychiatric interventions. In: G. Thornicroft, C. Brewin, & J. Wing, eds. *Measuring Mental Health Needs*. London: Gaskell. pp.200-224.

Beekman, A.T., de Beurs, E., van Balkom, A.J., et al. 2000. Anxiety and depression in later life: co-occurrence and community of risk factors. *American Journal of Psychiatry*, 157, pp.89-95.

Behar, E., DiMarco, I.D., Hekler, E.B., et al. 2009. Current theoretical models of generalized anxiety disorder (GAD): conceptual review and treatment implications. *Journal of Anxiety Disorders*, 23(8), pp.1011-23.

Boddington, S. 2014. CBT with older people. In: A. Whittington, N. Grey, eds. *How to become a more effective CBT therapist: Mastering metacompetence in clinical practice*. Wiley-Blackwell.

Bond, F.W., Hayes, S.C., Baer, R.A., et al. 2011. Preliminary psychometric properties of the Acceptance and Action Questionniare - II: A revised measure of psychological flexibility and experiential avoidance. *Behavior Therapy, 42, pp*.676-688.

Boutron, I., Moher, D., Altman, D.G., et al., for the CONSORT group. 2008. Methods and processes of the CONSORT Group: example of an extension for trials assessing nonpharmacologic treatments. *Annals of Internal Medicine*. W60-W67.

Braun, V., & Clarke, V. 2006. Using thematic analysis in psychology. *Qualitative Research in Psychology*, 3(2), pp.77-101.

Brenes, G.A., Danhauer, S.C., Lyles, M.F., et al. 2015. Telephone-delivered Cognitive Behavioral Therapy and telephone-delivered nondirective supportive therapy for rural older adults with Generalized Anxiety Disorder: A randomized clinical trial. *JAMA Psychiatry*, 72(10), 1012-1020.

Buszewicz, M., Griffin, M., McMahon, E.M., et al. 2016. Practice nurse-led proactive care for chronic depression in primary care: A randomised controlled trial. *The British Journal of Psychiatry*. Epub ahead of print.

Bystritsky, A. 2006. Treatment-resistant anxiety disorders. *Molecular Psychiatry*, 11, pp.805–814.

Cairney, J., Corna, L.M., Veldhuizen, S., et al. 2008. Comorbid depression and anxiety in later life: patterns of association, subjective well-being, and impairment. *American Journal of Geriatric Psychiatry*,16, pp.201–208.

Caudle, D.D., Senior, A.C., Wetherell, J.L., et al. 2007. Cognitive errors, symptom severity, and response to cognitive behavior therapy in older adults with generalized anxiety disorder. *American Journal of Geriatric Psychiatry*, 15(8), pp.680-9.

Clarke, S., Kingston, J., James, K., et al. 2014. Acceptance and Commitment Therapy group for treatment-resistant participants: a randomized controlled trial. *Journal of Contextual Behavioral Science*, 3(3), pp.179–188.

Covin, R., Ouimet, A.J., Seeds, P.M., et al. 2008. A meta-analysis of CBT for pathological worry among clients with GAD. *Journal of Anxiety Disorders*, 22, pp.108–116.

Davison, T.E., Eppingstall, B., Runci, S. et al. 2016. A pilot trial of acceptance and commitment therapy for symptoms of depression and anxiety in older adults residing in long-term care facilities. *Aging & Mental Health*, 4, pp.1-8.

Devilly, G.J., & Borkovec, T.D. 2000. Psychometric properties of the credibility/expectancy questionnaire. *Journal of Behavioral Therapy and Experimental Psychiatry*, 31, pp.73–86.

EuroQol Group. 1990. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy*, 16(3), pp.199-208.

First, M., Spitzer, R., Gibbon, M., et al. 1995. *Structured clinical interview for DSM-IV Axis I disorders. Patient edition (SCID-I/P)*. New York, NY: Biometrics.

First, M., Spitzer, R., Gibbon, M., et al. 1997. *Structured clinical interview for DSM-IV personality disorder*. American Psychiatric Press: Washington, D.C.

Gonçalves, D.C., & Byrne, G.J. 2012. Interventions for generalized anxiety disorder in older adults: systematic review and meta-analysis. *Journal of Anxiety Disorders*, 26(1), pp.1-11.

Gould, R.L., Coulson, M.C. & Howard, R.J. 2012. Efficacy of cognitive behavioral therapy for anxiety disorders in older people: A meta-analysis and meta-regression of randomized controlled trials. *Journal of the American Geriatrics Society*, 60(2), pp.218-229.

Gould, R.L., Coulson, M.C., Patel, N., et al. 2014. Interventions for reducing benzodiazepine use in older people: meta-analysis of randomised controlled trials. *British Journal of Psychiatry*, 204(2), pp.98-107.

Guest, G., Bunce, A. & Johnson, L. (2006). How many interviews are enough? An experiment with data saturation and variability. *Field Methods*, 18(1), pp.59-82.

Hayes, S.C., Strosahl, K.D., & Wilson, K.G. 1999. *Acceptance and Commitment Therapy: An experiential approach to behavior change*. New York: The Guilford Press.

Hayes-Skelton, S.A., Roemer, L., & Orsillo, S.M. 2013. A randomized clinical trial comparing an acceptance-based behavior therapy to applied relaxation for generalized anxiety disorder. *Journal of Consulting and Clinical Psychology*, 81(5), pp.761-773.

Herdman, M., Gudex, C., Lloyd, A., et al. 2011. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life*, 20(10), pp.1727-36.

Hunot, V., Churchill, R., Silva de Lima, M., et al. 2007. Psychological therapies for generalised anxiety disorder. *Cochrane Database of Systematic Reviews*, 1:CD001848.

Isaacowitz, D.M., & Seligman, M.E. 2002. Cognitive style predictors of affect change in older adults. *International Journal of Aging and Human Development*, 54, pp.233–253.

Jones, S.L., Hadjistavropoulos, H.D., & Soucy, J.N. 2015. A randomized controlled trial of guided internet-delivered cognitive behaviour therapy for olderadults with generalized anxiety. *Journal of Anxiety Disorders*, 37, pp.1-9.

Jourdain, R., & Dublin, P. 2009. "Giving it space": A case study examining Acceptance and Commitment Therapy for health anxiety in an older male previously exposed to nuclear testing. *Clinical Case Studies*, 8, pp.210-225.

Kangas, M., McDonald, S. 2011. Is it time to act? The potential of acceptance and commitment therapy for psychological problems following acquired brain injury. *Neuropsychological Rehabilitation*, 21(2), pp.250-276.

Karlin, B.E., Walser, R.D., Yesavage, J., et al. 2013. Effectiveness of acceptance and commitment therapy for depression: comparison among older and younger veterans. *Aging & Mental Health*, 17(5), pp.555-63.

Kohtala, A., Lappalainen, R., Savonen, L., et al. 2015. A four-session acceptance and commitment therapy based intervention for depressive symptoms delivered by masters degree level psychology students: a preliminary study. *Behavioural and Cognitive Psychotherapy*, 43(3), pp.360-73.

Laidlaw K, & Kishita N. 2015. Age appropriate augmented CBT for enhancing treatment outcome with older people. *GeroPsych, 28, pp.57-66*.

Lanouette, N., & Stein, M. 2013. Advances in the Management of Treatment-Resistant Anxiety Disorders. *Psychiatry Online*. http://focus.psychiatryonline.org/article.aspx?articleID=53282.

Lappalainen, R., Lehtonen, T., Skarp, E., et al. 2007. The impact of CBT and ACT models using psychology trainee therapists: a preliminary controlled effectiveness trial. *Behavior Modification*, 31(4), pp.488-511.

Lenze, E.J., Hickman, S., Hershey, T., et al. 2014. Mindfulness-based stress reduction for older adults with worry symptoms and co-occurring cognitive dysfunction. *International Journal of Geriatric Psychiatry*, 29(10), pp.991–1000.

Lenze, E.J., Mulsant, B.H., Shear, M.K., et al. 2001. Comorbidity of depression and anxiety disorders in later life. *Depression and Anxiety*, 14(2), pp.86-93.

Livingston, G.A., et al. 2014. *START (STrAtegies for RelaTives) study: a pragmatic randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of a manual-based coping strategy programme in promoting the mental health of carers of people with dementia*. HTA 08/14/06.

Livingston, G.A., et al. 2014. *The MARQUE project: Managing agitation and raising quality of life. A project to improve quality of life in people with moderate or severe dementia*. ESRC ES/L001780/1.

McCracken, L.M., & Jones, R. 2012. Treatment for chronic pain for adults in the seventh and eighth decades of life: a preliminary study of Acceptance and Commitment Therapy (ACT). *Pain Medicine*, 13(7), pp.860-7.

Medical Research Council. 2008. *Developing and evaluating complex interventions*. London: New guidance.

Meyer, T.J., Miller, M.L., Metzger, R.L., et al. 1990. Development and validation of the Penn State Worry Questionnaire. *Behaviour Research and Therapy*, 28, pp.487-495.

Miller, M.D., Paradis, C.F., Houck, P.R., et al. 1992. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Research*, 41, pp.237–248.

Mohlman, J., Gorenstein, E.E., Kleber, M., et al. 2003. Standard and enhanced cognitive-behavior therapy for late-life generalized anxiety disorder - Two pilot investigations. *American Journal of Geriatric Psychiatry*, 11, pp.24-32.

Mohlman, J., & Gorman, J.M. 2005. The role of executive functioning in CBT: a pilot study with anxious older adults. *Behaviour Research and Therapy*, 43, pp.447-465.

Molloy, D.W., Alemayehu, E., & Roberts, R. 1991. Reliability of a Standardized Mini-Mental State Examination compared with the traditional Mini-Mental State Examination. *American Journal of Psychiatry*, 148(1), pp.102–105.

National Institute for Health and Clinical Excellence. 2011. *Clinical guideline CG113: Generalised anxiety disorder and panic disorder in adults: management*.

Nezu, A., & Nezu, C. 2008. *Evidence-based outcome research: A practical guide to conducting randomized controlled trials for psychosocial interventions*. New York: Oxford University Press.

Oei TP, & Green AL. 2008. The Satisfaction with Therapy and Therapist Scale-Revised (STTS-R) for group psychotherapy: Psychometric properties and confirmatory factor analysis. *Professional Psychology Research and Practice*, 39(4), 435-42.

Osborn, D., Burton, A., Walters, K., et al. 2016. Evaluating the clinical and cost effectiveness of a behaviour change intervention for lowering cardiovascular disease risk for people with severe mental illnesses in primary care (PRIMROSE study): study protocol for a cluster randomised controlled trial. *Trials*, 17, 80.

Pachana, N.A., Byrne, G.J., Siddle, H., et al. 2007. Development and validation of the Geriatric Anxiety Inventory. *International Psychogeriatrics*, 19(1), pp.103-14.

Petkus, A.J, & Wetherell, J.L. 2013. Acceptance and Commitment Therapy with Older Adults: Rationale and Considerations. *Cognitive and Behavioral Practice*, 20(1), pp.47-56.

Plumb, J.C., & Vilardaga, R. 2010. Assessing treatment integrity in Acceptance and Commitment Therapy: Strategies and suggestions. *International Journal of Behavioral Consultation and Therapy, 6, pp*.263-295.

Porensky, E.K., Dew, M.A., Karp, J.F. et al. 2009. The burden of late-life generalized anxiety disorder: Effects on disability, health-related quality of life, and healthcare utilization. *American Journal of Geriatric Psychiatry*,17, pp.473–482.

Prina, A.M., Marioni, R.E., Hammond, G.C., et al. 2014. Improving access to psychological therapies and older people: findings from the Eastern Region. *Behaviour Research and Therapy*, 56, pp.75-81.

Roemer, L., & Orsillo, S.M. 2002. Expanding our conceptualization of and treatment for generalized anxiety disorder: integrating mindfulness/acceptance-based approaches with existing cognitive behavioral models. *Clinical Psychology: Science and Practice*, 9, pp.54–68.

Roemer, L., & Orsillo, S.M. 2005. An acceptance-based behavior therapy for generalized anxiety disorder. In: S.M. Orsillo & L. Roemer, eds. *Acceptance and mindfulness-based approaches to anxiety: conceptualization and treatment*. New York: Springer. pp. 213–240.

Roemer, L., Orsillo, S.M., & Salters-Pedneault, K. 2008. Efficacy of an acceptance-based behavior therapy for generalized anxiety disorder: evaluation in a randomized controlled trial. *Journal of Consulting and Clinical Psychology*, 76, pp.1083-1089.

Roemer, L., & Orsillo, S.M. 2007. An open trial of an acceptance-based behavior therapy for generalized anxiety disorder. *Behavior Therapy*, 38, pp.72–85.

Royal College of Psychiatrists. 2013. *Report of the Second Round of the National Audit of Psychological Therapies (NAPT)*. London: Healthcare Quality Improvement Partnership.

Schaub, R.T., & Linden, M. 2000. Anxiety and anxiety disorders in the old and very old: results from the Berlin Aging Study (BASE). *Comprehensive Psychiatry*, 41(Suppl. 1), pp.48–54.

Serfaty, M.A., Haworth, D., Blanchard, M., et al. 2009. Clinical effectiveness of cognitive behaviour therapy, versus control treatment or treatment as usual for depressed older people in general practice. *Archives of General Psychiatry*, 66(12), pp.1332-40.

Serfaty, M. et al. 2014. *The addition of ACT or a Talking Control to treatment as usual for the management of dysfunction in advanced cancer: a feasibility randomised controlled trial (CanACT)*. http://www.nihr.ac.uk/funding/funded-research/funded-research.htm?postid=1959.

Sharp, K. 2012. A review of Acceptance and Commitment Therapy with older adults. *International Journal of Psychology & Psychological Therapy*, 12(3), pp.359-372.

Sheehan. D.V., Lecrubier, Y., Harnett-Sheehan, K., et al. The Mini International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview. J. Clin Psychiatry, 1998;59(suppl 20):22-33.

Smout, M.F., Hayes, L., Atkins, P.W.B., et al. 2012. The empirically supported status of acceptance and commitment therapy: An update. *Clinical Psychologist*, 16(3), pp.97–109.

Spitzer, R.L., Kroenke, K., Williams, J.B., et al. 2006. A brief measure for assessing generalized anxiety disorder**:** the GAD-7**.** *Archives of Internal Medicine*, 166(10), pp.1092-1097.

Stanley, M.A., Beck, J.G., & Glassco, J.D. 1996. Treatment of generalized anxiety in older adults: A preliminary comparison of cognitive-behavioral and supportive approaches. *Behavior Therapy*, 27, pp.565-581.

Stanley, M.A., Beck, J.G., Novy, D.M., et al. 2003. Cognitive-behavioral treatment of late-life generalized anxiety disorder. *Journal of Consulting and Clinical Psychology*, 71, pp.309-319.

Stanley, M.A., Wilson, N.L., Amspoker, A.B., et al. 2014. Lay providers can deliver effective cognitive behavior therapy for older adults with generalized anxiety disorder: a randomized trial. *Depression and Anxiety*, 31(5), pp.391-401.

Stanley, M.A., Wilson, N.L., Novy, D.M., et al. 2009. Cognitive Behavior Therapy for Generalized Anxiety Disorder among older adults in primary care: A randomized clinical trial. *Journal of the American Medical Association*, 301, pp.1460-1467.

Teare, M.D., Dimairo, M., Shephard, N., et al. 2014. Sample size requirements to estimate key design parameters from external pilot randomised controlled trials: a simulation study. *Trials*, 15(1), p.264.

Tong, A., Sainsbury, P., & Craig, J. 2007. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*, 19(6), pp.349-357.

Twohig, M.P., Hayes, S.C., Plumb, J.C., et al. 2010. A randomized clinical trial of acceptance and commitment therapy versus progressive relaxation training for obsessive-compulsive disorder. *Journal of Consulting and Clinical Psychology*, 78(5), pp.705-16.

van Balkom, A.J., Beekman, A.T., de Beurs, E., et al. 2000. Comorbidity of the anxiety disorders in a community-based older population in The Netherlands. *Acta Psychiatrica Scandinavica*, 101, pp.37–45.

von Elm, E., Altman, D.G., Egger, M., et al. 2007. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Lancet*, 370(9596), pp.1453-1457.

Walser, R.D., Karlin, B.E., Trockel, M., et al. 2013. Training in and implementation of Acceptance and Commitment Therapy for depression in the Veterans Health Administration: therapist and patient outcomes. *Behaviour Research and Therapy*, 51(9), pp.555-63.

Walters, K., Rait, G., Griffin, M., et al. 2012. Recent Trends in the Incidence of Anxiety Diagnoses and Symptoms in Primary Care. *PLoS ONE*, 7(8), e41670.

Wetherell, J.L., Afari, N., Ayers, C.R., et al. 2011a. Acceptance and Commitment Therapy for generalized anxiety disorder in older adults: a preliminary report. *Behavior Therapy*, 42(1), pp.127-134.

Wetherell, J.L., Afari, N., Rutledge, T., et al. 2011b. A randomized, controlled trial of acceptance and commitment therapy and cognitive-behavioral therapy for chronic pain. *Pain*, 152, pp.2098–107.

Wetherell, J.L., Ayers, C.R., Sorrell, J.T., et al. 2009. Modular Psychotherapy for anxiety in older primary care patients. *American Journal of Geriatric Psychiatry*, 17, pp.483-492.

Wetherell, J.L., Gatz, M., & Craske, M.G. 2003. Treatment of generalized anxiety disorder in older adults. *Journal of Consulting and Clinical Psychology*, 71, pp.31-40.

Wetherell, J.L., Lenze, E.J., & Stanley, M.A. 2005. Evidence-based treatment of geriatric anxiety disorders. *The Psychiatric Clinics of North America*, 28, pp.871-896.

Wetherell, J.L., Petkus, A.J., Alonso-Fernandez, M., et al. 2015. Age moderates response to acceptance and commitment therapy vs. cognitive behavioral therapy for chronic pain. *International Journal of Geriatric Psychiatry*. Epub ahead of print.

Wetherell, J.L., Petkus, A.J., & Thorp, S.R. 2013. Age differences in treatment response to a collaborative care intervention for anxiety disorders. *British Journal of Psychiatry*, 203(1), pp.65-72.

Wetherell, J.L., Petkus, A.J., White, K.S., et al. 2013. Antidepressant medication augmented with cognitive-behavioral therapy for generalized anxiety disorder in older adults. *American Journal of Psychiatry*, 170(7), pp.782-789.

Wetherell, J.L., Stoddard, J.A., White, K.S., et al. 2011. Augmenting antidepressant medication with modular CBT for geriatric generalized anxiety disorder: a pilot study. *International Journal of Geriatric Psychiatry*, 26(8), pp.869–875.

Wetherell, J.L., Thorp, S.R., Patterson, T.L., et al. 2004. Quality of life in geriatric generalized anxiety disorder: A preliminary investigation. *Journal of Psychiatric Research*, 38, pp.305–312.

Wolitzky-Taylor, K.B., Castriotta, N., Lenze, E.J., et al. 2010. Anxiety disorders in older adults: A comprehensive review. *Depression and Anxiety*, 27, pp.190–211.

Yesavage, J.A., Brink, T.L., Rose, T.L., et al. 1983. Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research*, 17, pp.37-49.

Zargar, F., Farid, A.A.A., Atef-Vahid, M., et al. 2012. Effect of acceptance-based behavior therapy on severity of symptoms, worry and quality of life in women with generalized anxiety disorder. *Iranian Journal of Psychiatry and Behavioral Sciences*, 6(2), pp.23-32.

Appendix 4 – Schedule of assessments

	Phase 1: Screening	Phase 1: Manual development		Phase 2: Screening & baseline Ax	Phase 2: Intervention								Phase 2: Follow-up Ax
Visit No	1	2	3	1	2-3	4-5	6-7	8-9	10-11	12-13	14-15	16-17	18
Day(s)	1	2	3	1	1-2	3-4	5-6	7-8	9-10	11-12	13-14	15-16	1
Window of flexibility for visits	N/A	e.g. +/- 2 weeks	e.g. +/- 2 weeks	N/A	e.g. +/- 2 weeks	e.g. +/- 2 weeks	e.g. +/- 2 weeks	e.g. +/- 2 weeks	e.g. +/- 2 weeks	e.g. +/- 2 weeks	e.g. +/- 2 weeks	e.g. +/- 2 weeks	e.g. +/- 2 weeks
Informed consent	X			X									
GAD-7	X			X									
MINI	X			X									
SCID	X			X									
SMMSE	X			X									
Eligibility confirmation	X			X									
GAI				X									X
PWSQ				X									X
GDS-15				X									X
EQ-5D-5L				X									X
CSRI				X									X
AAQ-II				X									X
STTS-R													X
CEQ					X								
Qualitative interview		X	X										X
Intervention					ACT+	ACT+	ACT+	ACT+	ACT+	ACT+	ACT+	ACT+	
AE review	X			X	X	X	X	X	X	X	X	X	X

Note: AAQ-II = Acceptance and Action Questionnaire-II; ACT+ = Acceptance and Commitment Therapy plus usual care; AE = adverse events; Ax = assessment; CEQ = Credibility/Expectancy Questionnaire; CSRI = Client Service Receipt Inventory; GAD-7 = Generalized Anxiety Disorder-7; GAI = Geriatric Anxiety Inventory; GDS-15 = Geriatric Depression Scale-15; MINI = MINI International Neuropsychiatric Interview; PSWQ = Penn State Worry Questionnaire; SCID = Structured Clinical Interview for DSM-IV Axis II Disorders; SMMSE = Standardised Mini-Mental State Examination; STTS-R = Satisfaction with Therapy and Therapist Scale-Revised.