CONTACT-GAD

FULL STUDY TITLE
A randomised CONtrolled trial of Tailored Acceptance and Commitment Therapy for older people with treatment resistant Generalised Anxiety Disorder (CONTACT-GAD)

SHORT STUDY TITLE / ACRONYM
Acceptance and commitment therapy for older people with treatment resistant generalised anxiety disorder (CONTACT-GAD)

RESEARCH REFERENCE NUMBERS

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Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Date: 11/12/2023

Signature: 

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Position: Sponsorship Officer.....

UK Chief Investigator:

Date: 11/12/2023

Signature: 

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Name: (please print): Rebecca Gould

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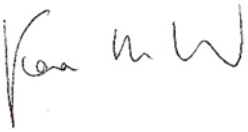
Australian Chief Investigator (on behalf of Australian Sponsor):

Date: 20/01/2023

Signature: 

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Name: (please print): Viviana Wuthrich

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Sheffield Clinical Trials Research Unit (CTRU)

A randomised CONtrolled trial of Tailored Acceptance and Commitment Therapy for older people with treatment resistant Generalised Anxiety Disorder (CONTACT-GAD)

Acceptance and Commitment Therapy for older people with treatment resistant generalised anxiety disorder / CONTACT-GAD

This document describes a trial, and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial.

List of contents

Abbreviations

ACT	Acceptance and Commitment Therapy
AE	Adverse Event
ACT-FM	ACT Fidelity Measure
ANZCTR	Australian New Zealand Clinical Trials Registry
CI	Chief Investigator
CIRS-G	Cumulative Illness Rating Scale-Geriatrics
CRF	Case Report Form
CSQ-8	Client Satisfaction Questionnaire-8
CSRI	Client Service Receipt Inventory
CNSGP	Clinical Negligence Scheme for General Practice
CompACT	Comprehensive Assessment of Acceptance and Commitment Therapy Processes
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
GAD	Generalised anxiety disorder
GAD-2	Generalised Anxiety Disorder Assessment-2
GAD-7	Generalised Anxiety Disorder Assessment-7
GDS-15	Geriatric Depression Scale-15
G-BO	Goal-based Outcomes tool
HRA	Health Research Authority
HREC	Human Research Ethics Committee
HTA	Health Technology Assessment
IAPT	Improving Access to Psychological Therapies
ICECAP-O	ICEpop CAPability measure for Older people
IPDS	Iowa Personality Disorder Screen
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
MINI	Mini-International Neuropsychiatric Interview
MQOL-R	McGill Quality of Life Questionnaire-Revised
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Clinical Excellence
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
R&D	Research and Development
REC	Research Ethics Committee
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIV	Site Initiation Visit
SMMSE	Standardised Mini-Mental State Examination
SOP	Standard Operating Procedure
TMG	Trial Management Group
TR-GAD	Treatment resistant generalised anxiety disorder
TSC	Trial Steering Committee
UCL	University College London

Key study contacts

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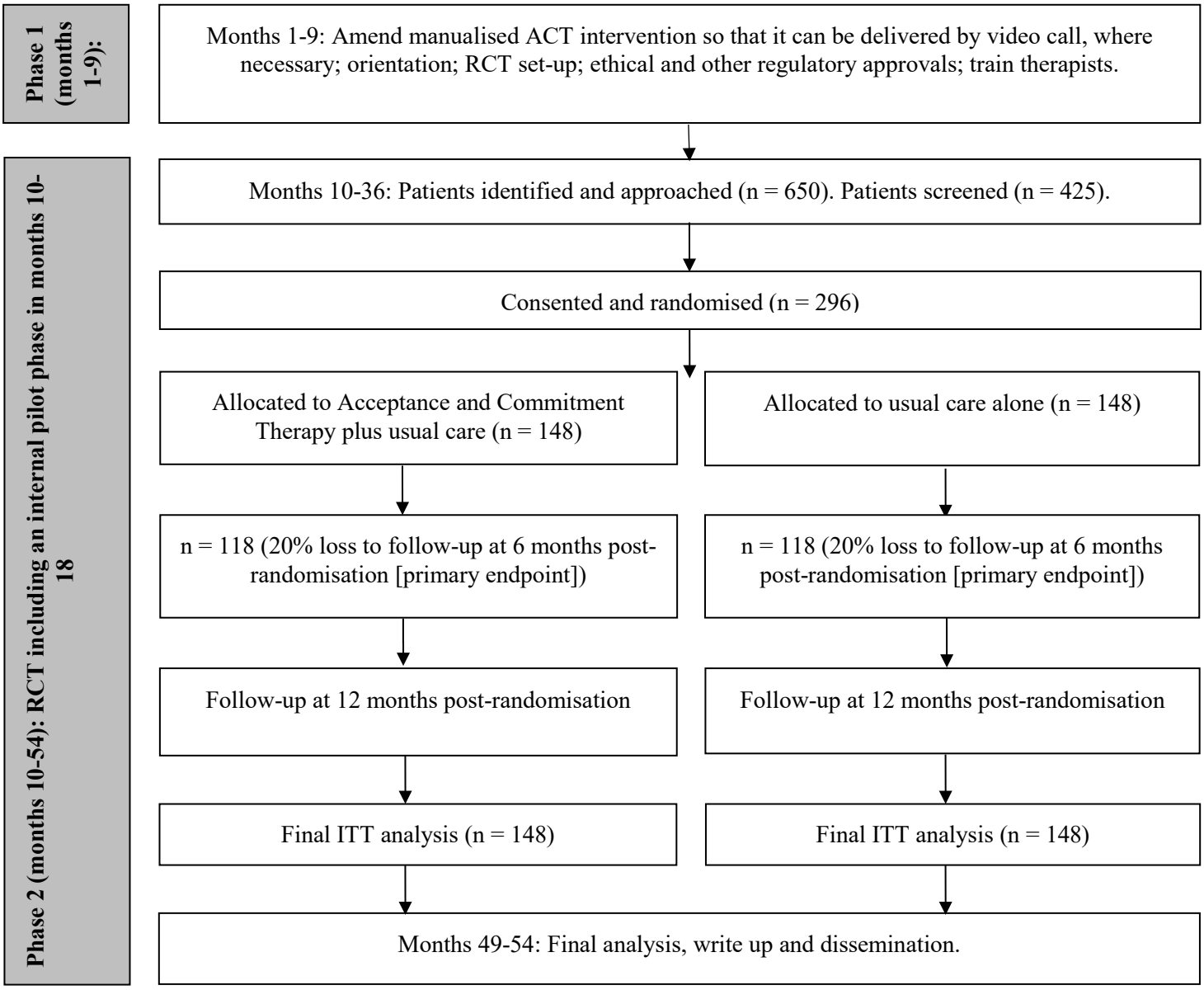
Trial summary

Study Title	A randomised CONtrolled trial of Tailored Acceptance and Commitment Therapy for older people with treatment resistant Generalised Anxiety Disorder (CONTACT-GAD).
Short title	Acceptance and commitment therapy for older people with treatment resistant generalised anxiety disorder (CONTACT-GAD).
Study Design	Randomised controlled trial.
Study Participants	People aged ≥60 years with treatment resistant generalised anxiety disorder (TR-GAD) that has failed to respond adequately to pharmacotherapy and/or psychotherapy treatment, as described in step 3 of the UK's stepped care model for GAD. GAD that has failed to respond adequately will be defined as continued symptoms of GAD that are still causing difficulties. Those who have been offered pharmacotherapy and/or psychotherapy treatment and did not want to start it or continue it and are still symptomatic will also be included in this definition. An equivalent definition will be used in Australia.
Planned Size of Sample (if applicable)	296 (218 participants in the UK and 78 in Australia).
Follow up duration (if applicable)	12 months.
Planned Study Period	01/08/2022-31/01/2027.
Research Question/Aim(s)	What is the clinical and cost effectiveness of tailored Acceptance and Commitment Therapy (ACT) plus usual care in comparison to usual care alone for reducing anxiety in older people with TR-GAD? The objectives are: 1) To adapt a previously developed intervention and all study procedures so that the trial can be delivered 100% remotely, where necessary; 2) To obtain definitive estimates of the clinical and cost effectiveness of tailored ACT plus usual care compared to usual care alone for older people with TR-GAD in an RCT with a 9-month internal pilot phase; 3) To collect qualitative and quantitative data from older people with TR-GAD and therapists to examine perceived mechanisms of impact, facilitators of and barriers to implementation, and the context in which the intervention is delivered; 4) To use qualitative and quantitative findings to make further refinements to the intervention at the end of the trial, particularly with respect to implementation in clinical practice; 5) To engage the public, stakeholders (including NICE, NHS England, NHS clinical commissioners, Ministry of Health (Australia) and other policy makers) and mental health services in order to ensure readiness for implementation in clinical practice (if ACT is found to be effective).
Keywords	Acceptance and Commitment Therapy, treatment-resistant generalised anxiety disorder, older people

Study flowchart



Protocol version history

Version number	Date	Protocol update finalised by (insert name of person):	Reasons for update
2.0	30.03.2023	Rebecca Gould	Minor clarifications and changes to secondary outcome measures
2.1	17.07.2023	Rebecca Gould	Minor clarification to section 4.2.1, details of electronic consent procedure added to section 4.4 and change to how SAEs will be assessed for expectedness in section 8.2
2.2	16.10.2023	Rebecca Gould	Minor clarification to how consent forms are reviewed as a part of monitoring in section 11.3
2.3	11.12.2023	Rebecca Gould	Minor clarifications outlining the use of Join Dementia Research and that participant-facing documents will be translated in section 4.3.1

STUDY PROTOCOL
A randomised CONtrolled trial of Tailored Acceptance and Commitment Therapy for older people with treatment resistant Generalised Anxiety Disorder (CONTACT-GAD)

1. Introduction

This study has been developed in response to a Commissioned Call by the National Institute for Health Research Health Technology Assessment (HTA) Programme to evaluate the clinical and cost-effectiveness of a psychological intervention for treatment resistant generalised anxiety disorder (TR-GAD) in older people within a randomised controlled trial (RCT).

1.1 Background

Generalised anxiety disorder (GAD) is the most common anxiety disorder in older people, with an estimated prevalence of up to 11% (1). It is characterised by excessive anxiety and worry, including feelings of fear, dread, and uneasiness, which is experienced as being difficult to control, on most days for at least six months (2). It may persist for decades and is associated with a range of negative outcomes, including poor health-related quality of life (QoL), as well as increased disability, healthcare use and functional limitations (3). Comorbidity with other mental health problems is common and associated with even poorer outcomes (4–7). For example, comorbid anxiety and depression are associated with more severe somatic symptoms, poorer social functioning, greater suicidal ideation, and greater prescription of benzodiazepines, as well as poorer treatment response (8,9). Several factors are associated with treatment-resistant anxiety including comorbid physical and mental health conditions, noncompliance, and environmental stressors (8).

National Institute for Health and Clinical Excellence (NICE) guidelines recommend a stepped care approach to the management of GAD in the UK (10). Step 1 comprises identification and assessment, followed by education and active monitoring within primary care. If unsuccessful, Step 2 involves low-intensity psychological interventions, such as guided self-help based on cognitive behavioural therapy (CBT) and psychoeducational groups, within primary care. Should symptoms persist or if there is marked functional impairment, then Step 3 comprises pharmacotherapy (e.g. selective serotonin reuptake inhibitors) and/or high-intensity, individual psychotherapy (either CBT or applied relaxation). If symptoms still persist, then Step 4 involves a referral to specialist mental health services (usually in secondary care) for assessment and treatment. Recommended treatment options include offering interventions from Steps 1-3 that have been previously declined and offering combination therapy.

GAD that does not respond to first-line treatments, such as antidepressants and conventional CBT, is also known as TR-GAD. There is no universally agreed definition of TR-GAD (11); the HTA Commissioned Call stated that when GAD fails to respond to treatment after completing the first three steps of stepped care then it can be considered treatment resistant. It has been shown that many older people with GAD find first-line treatments such as antidepressants, CBT or applied relaxation to be either ineffective, lack acceptability (e.g. due to side-effects) or unable to produce sustained benefit (12), leaving clinicians uncertain as to how to best manage this condition. Unfortunately, there is a lack of evidence to guide the management of TR-GAD in older people in the NHS and considerable unmet need. Consequently, developing treatment strategies that are acceptable and clinically effective for older people with TR-GAD is a public and mental health priority, particularly as the population ages (13).

A systematic review identified no RCT or observational study of pharmacotherapy or psychotherapy for treatment resistant anxiety in older people (14). To the authors' knowledge, our previous feasibility study of Acceptance and Commitment Therapy (ACT) for older people with TR-GAD (12,15,16), is the only study to have developed and evaluated a psychological intervention specifically for older people with TR-GAD. Systematic, qualitative methods were used, alongside public involvement, to build upon a protocol based on ACT that had been previously piloted with 7 older people with GAD (but not specifically TR-GAD) (17). Semi-structured interviews and a focus group were conducted with 15 older people with TR-GAD and 36 healthcare professionals who worked with older people with TR-GAD to: i) develop and tailor an ACT intervention to the specific psychological, physical and cognitive needs of older people with TR-GAD; and ii) ensure that it was suitable for delivery within the NHS (12). The intervention was then modified in order to improve its acceptability to this population, based on the results of further semi-structured qualitative interviews with older people with TR-GAD and consultations with a Public Involvement group, academic clinicians and study therapists. Finally, the intervention's acceptability and feasibility was assessed in an uncontrolled, feasibility study of 37 older people with TR-GAD (15).

High levels of feasibility in terms of recruitment (93% of the target sample size [37/40]) and retention at the final follow-up assessment (81% [30/37]) were shown. In addition, there was evidence of high levels of acceptability in terms of session attendance (70% [26/37] attended 10 or more sessions out of a possible 16), and adequate levels of satisfaction with therapy (60% [18/30] gave a rating of ≥21/30 on the Satisfaction with Therapy subscale – there is no set definition of satisfactory on this subscale, but a score of 18 corresponds to rating all items as neither satisfied nor dissatisfied). Although not powered to examine clinical effectiveness, efficacy signals in anxiety, depression and psychological flexibility (the aspect of psychological wellbeing targeted by ACT and the postulated mechanism of effect) from baseline to 20 weeks were demonstrated. Reliable improvements in scores (i.e. greater in magnitude than could be explained by measurement error or artefacts of repeated measurement) were found in 45% of participants on the Geriatric Anxiety Inventory, and in 24% of participants on the Geriatric Depression Scale-15 and the Acceptance and Action Questionnaire-II. Furthermore, changes in psychological flexibility were significantly associated with changes in anxiety, depression and worry. These results were particularly impressive since all participants had GAD that had failed to respond to prior pharmacological and/or psychological therapies for GAD, and little spontaneous change would be expected in this population. It was concluded that a full-scale RCT of ACT for older people with TR-GAD is warranted.

1.2 Rationale

ACT is an acceptance-based behaviour therapy (18), that is an alternative to first-line psychotherapies such as conventional CBT or applied relaxation and is not part of the current care pathway in the UK for older people with TR-GAD. ACT takes a different approach to first-line psychotherapies. CBT and applied relaxation focus on finding ways to control emotions and bodily sensations and challenge negative thoughts that accompany anxiety. In contrast, ACT is focused on increasing personally meaningful behaviour in the presence of distress and symptoms (though distress or symptoms may improve as a product of reducing the struggle with these experiences). It uses acceptance, mindfulness and motivational techniques to reduce unhelpful attempts to control negative thoughts, emotions and bodily sensations and increase engagement in life-enriching activities. These techniques include helping people to: i) be more open to and accepting of their internal experiences rather than engaging in ineffective struggles with them or fighting against them, as this serves to amplify such experiences; ii) become more aware of their experiences and focused on the here-and-now rather than dwelling on the past or worrying about the future; and iii) commit to doing things guided by what really matters to them and the type of person they want to be rather than by things they want to avoid.

ACT has an established evidence base in a range of mental and physical health conditions relevant to older people with TR-GAD, including anxiety, depression, chronic pain, substance use and transdiagnostic groups (19). Systematic reviews of ACT have reported improvements in a range of outcomes, including functioning, quality of life and mood (20–22). Further, ACT and ACT-based approaches have been shown to be as effective as CBT and applied relaxation for GAD in younger adults (17,23–26), but emerging evidence suggests that ACT may have advantages over conventional CBT through improved engagement, retention and durability of effects (17,26). A preliminary RCT in older people with GAD (but not specifically TR-GAD) reported improvements in worry/anxiety and depression with both ACT and CBT, but higher treatment completion rates with ACT (17). Furthermore, lower dropout and greater recovery rates have been found for ACT vs. CBT in adults with other treatment resistant mental health conditions (26).

ACT may be particularly suited to older people with TR-GAD for several reasons:
1) Later life brings unsolvable problems, such as multimorbidity (multiple comorbid chronic physical and mental health conditions) and multiple losses (to one's health, family, social network, role/identity and financial status). Control-orientated techniques used in conventional CBT, such as challenging thoughts or problem solving, can appear invalidating to older people and reduce engagement with therapy. Although excessive and unhelpful, worries about future losses may have an obvious basis in reality, and challenging them may be perceived negatively by older people;
2) Evidence suggests that control-orientated strategies (e.g. trying to eliminate unsolvable problems) are detrimental to older people's well-being (27), and those who adapt to changed circumstances rather than strive to control changes are more successful in meeting age-related challenges (28);
3) It is more feasible to address entrenched patterns of thought/behaviour with acceptance-based strategies than cognitive change strategies (29);
4) Older people with chronic conditions may be more likely to respond to ACT than CBT given that older people with chronic pain were more likely to respond clinically to ACT than CBT (30);
5) The transdiagnostic nature of ACT makes it uniquely able to efficiently address multimorbidity in older people.

Other interventions that could be considered for the management of TR-GAD include further or more intensive conventional CBT, applied relaxation, and/or collaborative care. However, offering more CBT or applied relaxation (even if augmented for older people) to those with TR-GAD, who have previously found this ineffective, may likely lead to more inadequate treatment response or refusal. Furthermore, evidence of smaller effect sizes in favour of conventional CBT for GAD in older people compared to working age adults (31–33) suggests that an alternative form of psychological intervention is required. Finally, an RCT of collaborative care in which older people with GAD were given the choice of CBT, pharmacotherapy or both was found to be no more effective than usual care (34).

2. Aims and objectives

2.1 Aims

To determine the clinical and cost effectiveness of tailored ACT plus usual care in comparison to usual care alone for reducing anxiety in older people with TR-GAD.

2.2 Objectives

1. To adapt our previously developed intervention (15) and all study procedures so that the trial can be delivered 100% remotely, where necessary.
2. To obtain definitive estimates of the clinical and cost effectiveness of tailored ACT plus usual care compared to usual care alone for older people with TR-GAD in an RCT with a 9-month internal pilot phase.
3. To collect qualitative and quantitative data from older people with TR-GAD and therapists to examine perceived mechanisms of impact, facilitators of and barriers to implementation, and the context in which the intervention is delivered.
4. To use qualitative and quantitative findings to make further refinements to the intervention at the end of the trial, particularly with respect to implementation in clinical practice.
5. To engage the public, stakeholders (including NICE, NHS England, NHS clinical commissioners, Ministry of Health (Australia) and other policy makers) and mental health services in order to ensure readiness for implementation in clinical practice (if ACT is found to be effective).

3. Trial design

CONTACT-GAD is an international, multicentre, single-blind, parallel, 2-arm RCT of tailored ACT plus usual care vs. usual care alone with a 9-month internal pilot phase in months 10-18. Stop/go criteria are listed in section 9.2. Participants will be recruited from sites in the UK and Australia. All study procedures will be designed so that they can be completed in person or remotely (via video call, phone, online or post), training can be completed via video call, and intervention delivery can be completed in person or via video call (depending on participant preferences and therapist availability) so that the trial can continue in the event of future COVID-19 pandemic waves and restrictions.

Completion of all study procedures via video call, phone, online or post and delivery of psychological and psychosocial interventions and training via video call has been successfully adopted in our ongoing clinical trials: ACT for people with motor neuron disease (many of whom are aged ≥60 years) (35), CBT for older people with anxiety and depression (36), problem adaptation therapy for people with dementia and depression (37), and a behavioural change intervention for older people with mild frailty (38).

4. Selection of participants

4.1 Settings

Participants will be recruited from primary care (GP practices, Improving Access to Psychological Therapies [IAPT] services, third sector organisations that receive primary care referrals and provide psychological therapies services such as MIND and equivalent healthcare providers in Australia), secondary care (community mental health teams and equivalent healthcare providers in Australia) and via self-referral from community settings in UK and Australia (e.g. voluntary organisations). As inclusion of recruitment sites in Australia will expand the generalisability of findings, at least 11 sites will be in the UK and 4 will be in Australia.

4.2 Eligibility criteria

4.2.1 Inclusion criteria

For older people with TR-GAD:
i) Aged ≥60 years;
ii) Diagnosis of GAD using the Mini-International Neuropsychiatric Interview (39);
iii) GAD that is 'treatment resistant', defined as GAD that has failed to respond adequately to pharmacotherapy and/or psychotherapy treatment, as described in step 3 of the UK's stepped care model for GAD (10). GAD that has failed to respond adequately will be defined as continued symptoms of GAD that are still causing difficulties. Those who have been offered pharmacotherapy and/or psychotherapy treatment and did not want to start it or continue it and are still symptomatic will also be included in this definition. An equivalent definition will be used in Australia. When determining whether GAD has failed to respond adequately to treatment, if a person has 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 TR-GAD;
iv) Living in the community (i.e. those living in domestic residences or assisted living facilities, but not care homes).

If psychiatric comorbidities are identified on the Mini-International Neuropsychiatric Interview, or prior to screening, then the participant will be asked which symptoms are the most distressing, most severe or of most concern to them. If they report that symptoms of GAD are most distressing, severe or of most concern, or that symptoms of GAD and the comorbid psychiatric disorder(s) are equally problematic, then they will be included in the study (if all other inclusion criteria are met and they consent to participation). If they report that symptoms of the comorbid psychiatric disorder(s) are most distressing, severe or of most concern then they will be excluded from the study and referred for appropriate treatment, if necessary, as participation in the study may delay treatment that may be more beneficial for them. The Mini-International Neuropsychiatric Interview has been modified for the purpose of this trial, with questions surrounding suicidality removed. The expression of suicidal ideation with active suicidal behaviours/plans and active intent is instead assessed via the Columbia-Suicide Severity Rating Scale Screener (40) (see section 4.2.2).

For study therapists completing the qualitative satisfaction questionnaire:
i) Aged ≥18 years;
ii) Therapists involved in intervention delivery within the CONTACT-GAD trial.

4.2.2 Exclusion criteria

For older people with TR-GAD:
i) Judged to lack capacity to provide fully informed written consent to participate in the trial;
ii) A diagnosis of dementia or intellectual disability using standard diagnostic guidelines, or clinically judged to have moderate or severe cognitive impairment (e.g. due to probable dementia, traumatic brain injury, stroke, etc);
iii) A diagnosis of an imminently life-limiting illness where they would not be expected to survive for the duration of the study;
iv) Expressing suicidal ideation with active suicidal behaviours/plans and active intent, as assessed using the Columbia-Suicide Severity Rating Scale Screener (40), for whom an inpatient admission would be more appropriate;
v) Currently receiving a course of formal psychological therapy delivered by a formally trained psychologist or psychotherapist (e.g. CBT, psychodynamic psychotherapy, systemic therapy, counselling, etc), or those who are unwilling to refrain from engaging in such formal psychological therapy should they be randomly allocated to the ACT arm;
vi) Self-report having received ACT in the FACTOID feasibility study (15);
vii) Having already been randomised in the CONTACT-GAD trial or living with another person who has already been randomised in the CONTACT-GAD trial;
viii) Taking part in clinical trials of other interventions for GAD.

It is common to include a psychotropic drug stabilisation period (e.g. a stable dose for at least two months) in eligibility criteria in psychotherapy trials. This is in order to allow for spontaneous recovery, and to control for the

potential confound of pharmacotherapy on psychological wellbeing. However, this will not be included as: a) spontaneous recovery in those with TR-GAD that has failed to respond to treatment in Steps 1-3 of the stepped care approach for GAD is extremely unlikely; and b) previous studies have shown that a drug stabilisation period can negatively impact on recruitment as it can take months to achieve this and people can be unwilling to wait for this to be completed. Service users are frequently referred to secondary care services 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. As this is intended to be a pragmatic therapy that is offered clinically in a population whose anxiety may drive multiple medication changes, all psychotropic drug use will be monitored and reported in data analyses.

4.3 Participant identification and screening

4.3.1 For older people with TR-GAD

Potential participants will be recruited via referrals from primary care (GP surgeries, GP list searches, IAPT) services and equivalent healthcare providers in Australia) and secondary care (Community Mental Health Teams for older people and equivalent healthcare providers in Australia), and via self-referral from the community. Potential participants will be identified and approached about the study in one of four ways:

Identification method 1: Clinicians from GP surgeries, IAPT services and Community Mental Health Teams (or the equivalent in Australia) will identify and approach potentially eligible participants and seek verbal consent for a member of the local research team (e.g. site staff identified on the delegation log) or central research team (e.g. research assistant identified on the delegation log) to contact them.

As noted above, many older people who meet diagnostic criteria for GAD are referred to primary and secondary care services with a diagnosis of major depression and comorbid anxiety or mixed anxiety and depression rather than GAD. Consequently, clinicians in the services noted above or a member of the local or central research team will be asked to pre-screen service users who are referred with these diagnoses (rather than GAD) using the Generalized Anxiety Disorder-2 (GAD-2), if they provide verbal consent to this. The GAD-2 is a 2-item version of the GAD-7 that is used to identify GAD in primary care and has good sensitivity and specificity (41). For any service user scoring ≥2 points on this scale (the validated cut-off score in older people that indicates further investigation is needed (42)), the member of the research team or clinician will ask the service user to complete the Patient Health Questionnaire-2 (PHQ-2). This is a 2-item version of the PHQ-9 that is used to identify depression in primary care (43). If the PHQ-2 total score is higher than the GAD-2 total score then the clinician/member of the research team will ask the service user whether the symptoms of depression or GAD 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/member of the research team will discuss the study with them further. If symptoms of depression are most distressing, severe or of most concern to them then the clinician will refer them for appropriate treatment, if necessary.

Identification method 2: Participating GP practices (i.e. those who have expressed an interest in participating in research through the Clinical Research Networks and local contacts) will, with support from the central research team to create search terms, conduct searches of their electronic medical records to identify those with current and/or historic diagnoses of GAD and other chronic anxiety states using a broad list of Read codes (44). This is a hierarchical coding system used in the UK to record clinical information such as diagnoses. An equivalent system will be used in Australia. Postal invitations will then be sent out to identified potentially eligible participants, who will be invited to contact a member of the local or central research team if they are interested in finding out more about the trial. Searches and postal invitations will be supplemented by adding an alert and simple referral template to the software systems of participating 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 for a person aged ≥60 years. These strategies have been successfully employed for identifying participants through GP list searches in previous studies (45). The study will also be promoted through talks and presentations to GPs and in clinical team meetings, in which education about recognising GAD in older people will be provided as it is often underdiagnosed (46).

Identification method 3: In order that people can self-refer into the trial, leaflets, posters and advertisements will be distributed in GP surgeries, relevant voluntary sector organisations, and other community settings such as luncheon clubs and activity groups for older people and faith-based organisations. Leaflets will include the GAD-

2, and potential participants will be invited to contact a member of the local or central research team if they score ≥2 points on it and are interested in finding out more about the trial. In addition, the study will be promoted through talks and presentations at these settings, and through local Age UK group newsletters (or their equivalent in Australia). Where appropriate, local media or social media may be used to support recruitment. This may include the approved trial poster or leaflet being shared or an approved advertisement being placed in a newspaper or online. Contact details will be provided so that potential participants can contact a member of the local or central research team if they are interested in finding out more about the trial.

Identification method 4: People who have already provided consent for research contact within primary or secondary care services' local research registers or within databases of older people interested in research participation will be identified by clinicians using methods noted above. Clinicians will not need to seek verbal consent for a member of the local or central research team to contact them as potential participants will have consented to this as part of the consent for research contact process.

We will also be using Join Dementia Research (JDR) as a recruitment tool. This is an online self-registration service that enables volunteers with memory problems or dementia, carers of those with memory problems or dementia and healthy volunteers to register their interest in taking part in research. The purpose of JDR is to allow such volunteers to be identified by researchers as potentially eligible for their studies. Researchers can then contact volunteers, in line with the volunteers' preferred method of contact, to further discuss potential inclusion.

JDR is funded by Department of Health and Social Care working in partnership with the charities Alzheimer Scotland, Alzheimer's Research UK and Alzheimer's Society and is Health Research Authority (HRA) endorsed. The online service and all associated documentation, methods of contacting volunteers and handling of data, were reviewed by a specially convened HRA committee which included experts in research ethics, data protection and information governance. Formal endorsement was issued by the HRA in a letter dated 5 November 2019.

Screening: Once potential participants have been identified and verbal consent for contact has been obtained, a member of the local or central research team will discuss the trial with them, either in person or via video call, phone or email, depending on participant preference and research staff availability. The trial will be described to them and the potential participant will be given the opportunity to ask any questions or discuss any initial concerns. If they express an interest in participating in the trial, they will be asked to verbally consent to completing the GAD-2 screening questionnaire, unless the GAD-2 screening questionnaire has already been completed by the participant as a part of identification methods outlined above. If they score ≥2 points on the GAD-2 and if they continue to express an interest in participating in the trial then they will be given a Participant Information Sheet (PIS) either in person or via post or email. They will then be given as long as they feel is needed to consider the information prior to being contacted by a member of the local or central research team to determine whether they are still interested in participating in the trial. If they are then the member of the local or central research team will arrange a screening appointment, either in person or via phone or video call. Written informed consent will be sought from potentially eligible participants, as outlined in section 4.4, after which eligibility for inclusion in the study will be determined during a screening interview.

Promotional strategies: Previously successful promotional strategies for recruiting under-represented older people will be adopted in the study, including following recommendations from the TIBaR model (building up trust, offering incentives, identifying individual barriers and being responsive) and following up an initial expression of interest with up to four attempts at telephone contact (47). People from a broad range of diverse groups and under-represented populations (with respect to age, sex, religion, ethnicity, race, socio-economic status, sexual orientation, rural living status, etc) will be purposively recruited through methods such as those listed below. Promotional materials will be distributed that include contact details for the local research team, whereby individuals will self-refer and be directed to a suitable recruiting centre. The following strategies may be taken (with equivalent strategies in Australia):
1) Promoting the trial in local community groups and lunch/social clubs in order to identify participants aged ≥80 years old, as only 22% of participants in the FACTOID study were aged ≥80 years;
2) Building relationships with local community leaders in faith-based organisations to promote the trial;

3) Adopting the NIHR BAME toolkit (48) and focusing on strategies that are seen as appropriate by communities in order to recruit people from BAME groups;
4) Including UK recruitment sites with high scores on the Income Deprivation Affecting Older People Index (49) (at least 6 of the planned sites have local authority districts that are in the top 20 for 2019 with the highest proportions of older people in income deprivation in the UK) and including GPs who serve deprived areas such as those who are part of Deep End groups (50) in order to recruit from geographic areas with more deprivation;
5) Including recruitment sites from geographic populations with high prevalence of common mental health disorders that have been historically underserved by research activity in this field by using the NIHR's Research Targeting Tool (51);
6) Promoting the trial in local LGBTQ+ groups and online forums;
7) Building relationships with local community leaders of those indigenous to Australia;
8) Including recruitment sites with ethnically diverse populations and providing interpreters for those with limited or no spoken English skills who require them (see below);
9) Promoting the trial in local clubs and men's sheds for those who self-identify as male, as the majority of participants in the FACTOID study self-identified as female (81%);
10) Making local community announcements, as recommended by the Public Involvement Group involved in developing the application;
11) Promoting the trial through a snowballing approach of encouraging people to share information via word-of-mouth.

Those who speak English as a second language or who speak no English necessitating the use of an interpreter will not be excluded, but will complete study procedures, therapy sessions and outcome measures through interpreters (or through bilingual therapists, where possible), where necessary. As this is intended to be a pragmatic trial, the inclusion of interpreters will mimic the standard of care that is currently provided in the UK's NHS and in Australia, including for psychological therapy services. Translators will not be employed to translate therapy materials and outcome measures due to difficulties inherent in ensuring adequate cultural adaptation, translation and back-translation. Instead, previously translated versions of outcome measures will be used, where possible. In addition, learning from our trial of ACT in motor neuron disease (35) – where barriers around communication and cognitive capabilities have been overcome by adapting materials for those who cannot access complex information and training therapists to communicate ACT principles in ways that increase accessibility – will be applied to working with interpreters. Participant-facing documents such as the PIS, consent form, recruitment leaflet and recruitment poster will be translated into languages other than English where possible.

One benefit of including those with limited or no spoken English skills that necessitate the use of an interpreter is the potential generalisation of findings to a broader population. Previous research demonstrates that ACT shows cultural acceptability, having been successfully implemented across many countries worldwide, including countries such as Iran and India (52,53). However, in a heterogeneous group with respect to language and cultural background, potential difficulties with engagement and/or dilution of treatment effects due to inadequate translation of ACT concepts or metaphors by interpreters remains a challenge. Consequently, additional exploratory analyses will be undertaken to assess the consistency of treatment effects in those with limited or no spoken English skills.

4.3.2 For study therapists completing the qualitative satisfaction questionnaire

Therapists will be recruited from the group of study therapists who will be involved in delivering the ACT intervention to older people with TR-GAD. They will be approached about completing the qualitative satisfaction questionnaire by a member of the central research team. If they express an interest in completing the qualitative satisfaction questionnaire then the member of the central research team will discuss this with them via video call, telephone or email, depending on therapist preference. Completion of the qualitative satisfaction questionnaire will be described to them and therapists will be given the opportunity to ask any questions or discuss any concerns. If they express an interest in participating in this aspect of the trial then they will be given a relevant Participant Information Sheet (PIS). They will then be given as long as they feel is needed to consider the information prior to being contacted by a member of the central research team to determine whether they are still interested in completing the qualitative satisfaction questionnaire.

4.3.3 Commencement of recruitment

Recruitment of older people with TR-GAD and study therapists at a site will only commence when the study has:
i) Received Research Ethics Committee (REC) (UK) and Human Research Ethics Committee (Australia) approvals;
ii) Received Health Research Authority (HRA) (UK) approval;
iii) Received confirmation of capability and capacity from the individual participating NHS Trusts (or received equivalent organisation approval in Australia) and the site has completed a Site Initiation Visit;
iv) Received the green light from the Sponsor (or its delegated representative).

4.4 Informed consent procedures

Participants and therapists will be consented in line with the Sheffield Clinical Trials Research Unit (CTRU) Informed Consent Standard Operating Procedure (SOP). All potential participants will be given a relevant PIS and will have the opportunity to discuss the trial, ask questions and request further information for as long as needed before being asked to provide fully informed written consent or verbal consent (if verbal consent is being obtained by telephone or videoconference e.g. due to participant preference, research staff capacity or pandemic-related restrictions).

Where verbal consent is obtained by telephone or videoconference, the researcher will read each statement from the consent form and ask the potential participant to state whether or not they consent to the statement. The researcher will initial each box where consent is agreed. A copy of the consent form will be sent to the potential participant via email or post, along with the relevant information sheet, so that they can also read the statements as they are being read out aloud. Once all statements have been agreed to, the potential participant will state their name, and the date will be stated by the researcher obtaining consent. With the potential participant's agreement, the conversation regarding consent will be audio recorded using an encrypted digital voice recorder. Once the researcher has signed the consent form, a copy will be sent to the participant for their records, and the encrypted audio file will be uploaded to a secure server within UCL's Data Safe Haven. This is a system that satisfies the highest level of security requirements of NHS trusts.

Two options to provide digital consent will be offered if this is the preference of the potential participant. For a consent appointment by telephone or videoconference, a digital consent form will be emailed to the potential participant, who can complete the form electronically, provide a simple digital signature in the form of a typewritten signature, and return the form to the researcher. Alternatively, they will be emailed an individualised link to an online consent form via Qualtrics. The potential participant can complete the form electronically via a yes/no response to each consent statement and provide a simple digital signature in the form of a tick box and declaration and submit the form online. Finally, those participants who do not have access to the internet will be able to sign a paper copy of the consent form and return to a member of the local or central research team via post in a pre-paid envelope.

Potential participants will be asked to provide consent in accordance with the Mental Capacity Act (2005). It is expected that potential participants will be able to provide informed consent for participation, provided that appropriate time and care has been taken by the member of the local or central research team or research nurse from the Clinical Research Network to explain the research, and that the potential participant has sufficient time to make a decision and communicate this. Participants will not be included in the study if they are unable to provide fully informed consent for participation. It will be explained that participants are under no obligation to enter the trial and that they can withdraw at any time, without having to give a reason and without their subsequent care or legal rights being affected. It will be made clear to participants that no disadvantage will accrue if they choose not to participate in the trial. It is not expected that participants will lose the capacity to provide informed consent during the course of the trial. If they do, then they will be withdrawn from the trial. 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 trial.

It will be the responsibility of the Principal Investigator (PI), or a person delegated by the PI, to obtain written or verbal informed consent from each participant prior to participation in the trial, 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 PI/Co-Investigator on the delegation of tasks. Capacity to provide consent will be determined at the screening and baseline assessment. No trial procedures will

be conducted prior to the participant giving consent to participate in the trial. Screening and baseline assessments will only be completed after fully informed consent is given by the participant (either via written consent or verbal consent). A copy of the signed consent form will be given or sent to the participant by post, or by email for those received electronically. The original signed form will be retained in the trial file at the recruitment site.

Potential participants will be made aware, during screening, consent and in the PIS, of the importance of complete datasets and the impact that missing data has on a trial, as recommended (54). Prior to obtaining consent and entering the potential participant into the study, a member of the local or central research team will make it clear to the participant the number of follow-ups that will take place and the assessments that will be completed during these follow-ups. Where a potential participant expresses concern, the member of the local or central research team will talk through these concerns and explain why these assessments and/or follow-ups will take place. It will also be made clear that if a participant chooses to withdraw from treatment, they will still be asked to complete 6- and 12-month follow-up assessments. In addition, it will be made clear that if they choose to withdraw from the trial and not complete further follow-up assessments, any data already provided by the participant will remain in the full dataset for intent-to-treat analysis.

5. Assignment of interventions

5.1 Sequence generation

Eligible participants with TR-GAD will be randomised in a 1:1 ratio using a web-based, centralised randomisation system hosted by the Sheffield Clinical Trials Research Unit (CTRU). This system has user-restricted functionalities that grant access rights to specific areas that are appropriate depending on the roles in the trial. Details of the randomisation will be retained within the system. Randomisation will be stratified by recruitment site.

5.2 Allocation concealment

The allocation sequence will be hosted by the Sheffield CTRU in accordance with their standard operating procedures and will be held on a secure server. Access to the allocation sequence will be restricted to those with authorisation until recruitment and data collection are complete. Allocation concealment will be achieved by requiring the details of participants to be entered onto the system before the randomly allocated treatment is revealed.

5.3 Implementation

A CTRU statistician will set up the CTRU randomisation system, but neither statistician nor other trial team members will be able to view the randomisation list during the trial. Once the eligible participant provides fully informed consent and baseline measures have been taken, the participant will be randomised. A member of site staff, signed onto the delegation log (not the blind outcome assessor at the site), will log into the remote, secure internet-based randomisation system and enter basic demographic information, after which the allocation will be revealed. Participants and their GPs (or equivalent healthcare providers in Australia) will be informed of the allocation by telephone or letter by the member of site staff.

5.4 Blinding

At least one trial statistician will be blinded to allocation during the trial. The outcome assessor will be intended to be blind to treatment allocation for the duration of the trial. Participants, study therapists and clinicians will be aware of the treatment allocation for the trial.

The DMEC will have access to unblinded data at their request during the trial; these data will be prepared by the data management team in the CTRU, aided by another CTRU statistician not involved in the trial when required. The TMG and TSC data report will provide summary outcome data by site but not allocation arm. As such no member of the trial team other than data management will have access to outcomes in relation to the allocation arm until the end of the trial.

Any instances of un-blinding will be recorded, including information on who was un-blinded, the source of un-blinding, and the reason for un-blinding.

6. Trial arms

6.1 ACT plus usual care

6.1.1 Intervention

An ACT intervention that was previously developed for older people with TR-GAD and tested for feasibility within an uncontrolled feasibility study (12,15,16) will be evaluated in this trial. This is not part of the current care pathway for older people with TR-GAD. The intervention comprises a therapist manual, accompanying participant workbook and therapist training programme. Findings from qualitative interviews with older people with TR-GAD and healthcare professionals and previous recommendations (55) were used to ensure that it was tailored to the specific psychological, physical and cognitive needs of older people with TR-GAD and suitable for delivery within the NHS.

Frequency and duration of sessions: Participants will be offered up to 14 individual (i.e. one-to-one) sessions of tailored ACT over 6 months plus a booster session approximately 3-months post-intervention (i.e. approximately 3 months after the final ACT session), with each session lasting up to 1 hour. This is consistent with previous recommendations of 12-16 sessions of ACT for older people (55,56), as well as existing practice in Step 3 of the stepped care approach for GAD (10), which recommends 12-15 sessions of CBT or applied relaxation. The provision of up to 14 sessions allows 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 (57). The provision of a booster session at 3-months post-intervention in which ACT skills and strategies are reviewed will aid the consolidation and enactment of skills and strategies discussed in the sessions. The booster session will be conducted after the outcome assessment at 6 months follow-up in order to avoid biasing outcomes at this timepoint. There will be a phased ending to the sessions, such that they are approximately weekly for the first 12 sessions and then approximately fortnightly thereafter, as some older people with GAD can experience difficulties when therapy ends abruptly. Based on peer review feedback, partners or family members will be invited to attend all sessions, with the participant's consent. It will be emphasised that the sessions will be focused on the person with TR-GAD rather than the partner/family member.

Delivery of sessions: Sessions will be delivered in-person in the outpatient clinic, GP surgery or participant's home, or via video call or telephone call (where videoconference facilities are not available), depending on participant preference, therapist availability and service restrictions. Some of the primary and secondary care sites will act as the recruitment sites and some will act as Participant Identification Centres (PICs). This will increase the accessibility of the intervention, ensuring that it is available to those who are unable to travel due to physical and/or mental health issues or geographical distance (e.g. those in rural communities), as well as ensuring it can continue to be delivered in the event of future COVID-19 pandemic waves and restrictions. The platform of the video calls for intervention delivery will be in line with current clinical practice at the recruiting site. Mode of therapy delivery will be recorded as this may impact on the effectiveness of the intervention.

Session content: Sessions will be supported by an accompanying participant workbook comprising psychoeducation about GAD, summaries of key ACT concepts and skills, and home practice worksheets (with emphasis on practicing skills rather than writing down self-observations as some people do not like doing this). The first session will comprise an age-appropriate assessment aimed at developing a shared understanding of a person's current difficulties within a lifespan context, as well as biological, psychological, social and cultural factors that might be maintaining these difficulties within an ACT conceptualisation. Each subsequent session will be associated with a specific set of skills, metaphors, experiential exercises, audio files and home practice tasks designed to increase psychological flexibility (akin to coping or being more adaptable in conventional CBT). Each session will commence with a short mindfulness exercise designed to increase awareness of the present moment. This will be followed by a recap of the concepts and issues discussed in the previous session, as well as a discussion of the participant's experience of completing the home practice.

The rest of the session will be spent focusing on increasing psychological flexibility through six core evidence-based processes:

i) Acceptance or willingness: Reducing avoidance of difficult or uncomfortable experiences (e.g. thoughts, emotions, physical sensations, urges), where such behaviour is a barrier to life enriching activity. For example, by reducing attempts to try and control, change or get rid of such experiences (e.g. through excessive worrying or

planning in relation to “worst case scenarios”, keeping oneself excessively busy, substance misuse, seeking reassurance, avoiding stressful situations, avoiding making decisions, etc);
ii) Defusion: Reducing the degree to which people are caught up in unhelpful thoughts about worrying (e.g. “Worrying shows that I care”, “Worrying is going to kill me”), themselves (e.g. “I can’t cope”, “I can’t trust myself to make the right decision”), their situation (e.g. "It's hopeless", “What’s the point?”), shared generational cohort beliefs (e.g. "you can't teach an old dog new tricks") and intergenerational linkages (e.g. "I'm a burden on my family");
iii) Contact with the present moment: Reducing the amount of time people are "stuck in their head" ruminating about the past (e.g. “Have I done the wrong thing?”, “I shouldn’t have done that…”) or worrying about the future (e.g. “What if…?”);
iv) Self-as-context: Reducing the degree to which people are caught up in unhelpful self-narratives, for example, about their identity (e.g. "I’ve always been a worrier”, “I’m too old to change”) or changes in their roles (e.g. "I'm not the person I used to be", "I'm no longer needed");
v) Values: Helping a person to identify what really matters to them in their lives (e.g. family, community, spirituality, etc) rather than losing contact with this;
vi) Committed action: Helping a person to commit to doing personally meaningful activities guided by the things they value (e.g. spending quality time with their family in service of being a caring and loving mother) rather than the experiences they want to avoid.

One of the main aims of ACT is to help people “live better” rather than “feel better”, and so a key component that will run throughout each session is an exploration of the workability of attempts to try and control, change or get rid of worry and anxiety. That is, how these attempts have worked to get rid of anxiety, both in the short and longer term, and how they are helping the person to do the things that are important to them or to be the type of person they want to be alongside their difficult or uncomfortable experiences. Each session will end with a summary of what has been discussed, as well as a review of that week’s home practice. Home practice tasks will be set in collaboration with each participant, and will be adjusted to accommodate physical health problems using 'selective optimisation with compensation' principles.

Depending on the participant’s needs and goals, therapists will also be able to address key psychoeducational issues or skills deficits commonly associated with GAD in one of the sessions, including: i) establishing good sleep habits; ii) problem solving for external problems (but not internal problems such as difficult thoughts, emotions and sensations); and iii) graded exposure to worst case scenarios or feared situations, objects or internal experiences (where the emphasis is on increasing willingness to have difficult or uncomfortable experiences rather than reducing distress). The intervention also includes an optional protocol to help participants gradually withdraw from inappropriate prescription medication (such as benzodiazepines and other hypnotic drugs), over-the-counter medication (such as sedative antihistamines), alcohol and illicit substances, if they wish. The protocol addresses psychoeducation about substance misuse, the risks and benefits of this, and ways of reducing this. If participants consent to reduce their use of illicit or inappropriate drugs, they will be invited to engage in a gradual withdrawal program, alongside ACT. This withdrawal program would be conducted and monitored by their psychiatrist and/or GP (or equivalent healthcare provider in Australia) in line with current clinical practice at the recruiting site.

The final therapy session will include a review of skills developed in the sessions, any gains made and ways of maintaining these. Finally, a booster session at approximately 3-months post-intervention will review topics discussed in the final session, as well as identifying barriers to behavioural change and ways of overcoming them.

6.1.2 Therapists

Therapists will be Band 7 or Band 8 clinical psychologists, counselling psychologists, psychotherapists or CBT therapists (or their equivalent in Australia) who are based in primary or secondary care services, with ≥1 year experience of delivering psychotherapy interventions. Ideally, two or more therapists from each recruiting site will be identified, though this will vary across sites depending on therapist availability. Furthermore, ideally, therapists who have already received some training in ACT (e.g. through ACT training initiatives in some IAPT services) will be recruited. Therapists who have previously attended other ACT workshops will still be required to attend the study training in order to ensure consistency of training. However, as therapists are not routinely trained in this in the NHS, training using the programme developed in a previous feasibility study will be provided. Furthermore, although initial knowledge and/or experience of working with older people with TR-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 (i.e. in the pre-orientation phase) and on an ongoing basis thereafter, where

necessary. All therapists will attend a 4-day experiential ACT training workshop via video call, delivered by trained members of the research team with a minimum of five years' experience in delivering ACT, as well as experience of training therapists to deliver ACT in clinical trials. Training will be conducted via video call in order to overcome difficulties associated with therapists being located in geographically diverse regions across the UK and Australia. The flexibility and accessibility that videoconferencing offers will continue to be utilised to ensure that therapists who are unable to spend additional time travelling or having overnight stays due to caring responsibilities are able to participate in the trial.

Training will comprise a combination of didactic learning through teaching and demonstrations, experiential learning through the personal experience of ACT metaphors and exercises, and practical learning through roleplays with other therapists. Training on the specific application of ACT to older people with TR-GAD will be incorporated throughout the 4-day workshop. Training will also incorporate sessions on how to deliver ACT via video call and how to work with older people with hearing impairment via video call, based on the findings of a study examining how older people with hearing loss use videoconferencing technology (58). Training will include interested members of the Public Involvement Group, where possible. Following initial training, therapists will be asked to practice delivering ACT to one service user on their caseload, under supervision, before commencing intervention delivery in the RCT (assuming satisfactory competence in ACT delivery is achieved).

Two measures will be used to rate ACT competence. First, a validated ACT Knowledge Quiz comprising 16 multiple choice questions about ACT processes, where ACT competence will be defined as a score of >=50%. Second, a 6-item ACT scenario-based questionnaire that was developed in a trial of ACT for people with motor neuron disease, which will be adapted for older people with TR-GAD. Each item gives an example of what a participant might say in a session, asks the therapist to identify the psychologically inflexible process indicated by what has been said, and then consider how they might respond to what has been said in an ACT consistent way. A trained member of the research team will provide an overall rating of ACT consistency, ranging from 1 (not at all) to 5 (extensively). ACT competence will be defined as an overall score of ≥3 out of 5 (corresponding to at least satisfactory performance). If therapists do not demonstrate satisfactory competence on the ACT scenario-based questionnaire then they will be invited to review ACT training with ACT-trained members of the research team and will only be "passed" when they have demonstrated satisfactory competence on it. Therapists will also attend a 1-day top-up training course after 12 months to review and consolidate skills in delivering ACT to older people with TR-GAD. 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 (59), and is supported by evidence that ACT can be successfully delivered by novice therapists (15,17,60,61).

6.1.3 Supervision of therapists

Therapists will be invited to attend group supervision and consultation via video call on a fortnightly basis, though sessions will be provided weekly to make them as accessible as possible. Group supervision and consultation will be provided by trained members of the research team with a minimum of five years' experience in delivering ACT, as well as experience in supervising ACT, including within a clinical trial. Anonymised supervision notes will be recorded in each session and made available to both supervisors and therapists, and supervisors will observe some of each other's sessions to ensure that a consistent approach is used with therapists. This approach to supervision and consultation is being successfully used in an ongoing trial of ACT for people with motor neuron disease (35). In addition to group supervision and consultation via video call, therapists will be able to receive support through a secure, supervisor-moderated online forum. Therapists will be able to discuss anonymised issues arising in intervention delivery with supervisors and other therapists. The flexibility of this approach means that therapists will have the opportunity to receive supervisor and peer support between fortnightly group supervision and consultation sessions.

6.2 Usual care

All participants will receive all aspects of usual care, with the exception of courses of formal psychological therapies such as CBT for those receiving ACT. Usual care will comprise standard care as outlined in NICE clinical guideline 113 for GAD (10). This states that those who have an inadequate treatment response to Steps 1-3 of the stepped care approach should be referred to specialist mental health services (usually located within secondary care) for assessment and offered interventions from Steps 1-3 that have been previously declined or combination therapy. For those whose onset of GAD is more recent, it is likely that usual care will comprise care by a GP (or an equivalent healthcare provider in Australia) with multidisciplinary team input including assessment, psychotropic medication review and management, case management, and psychotherapy and/or occupational

therapy for a smaller proportion of participants within secondary care services. For those whose onset of GAD occurred in earlier life, usual care may simply include pharmacotherapy managed by GPs (or equivalent healthcare providers in Australia), as they may have already been offered or tried a variety of treatments within secondary care and discharged back to the GP. Usual care in Australia is similar to the UK and will comprise any or a combination of pharmacotherapy, supportive counselling by allied health staff and psychological therapy of various modalities. As some variations in usual care are likely across participants, this will be monitored using a modified form of the Client Service Receipt Inventory (62). Furthermore, as some variations in usual care may occur across recruiting sites, additional exploratory data analysis of this will be undertaken if there are substantial variations in the standard of usual care delivered across sites.

Those randomised to ACT will be asked to refrain from concurrent formal psychological therapies since this may lead to conflicts in therapeutic approaches and goals, for example, being instructed to challenge thoughts in CBT at the same time as being mindfully aware of thoughts in ACT. Other than this, no attempts will be made to actively discourage participants from seeking treatment outside of the study. Instead, usual care will be monitored using the modified Client Service Receipt Inventory, and additional exploratory data analysis assessing the impact of treatment for mood disorders received outside of the study will be undertaken if used by a substantial proportion of participants. Participants will be able to continue their receipt of ongoing psychotropic pharmacotherapy while receiving ACT plus usual care or usual care alone. Although it is anticipated that pharmacotherapy will be equal in both intervention groups, all psychotropic drug use will be monitored and recorded throughout the course of the trial (including changes to dose and frequency). Sensitivity analyses will examine the consistency of outcomes across psychotropic medication use.

6.3 Concomitant medication

For participants with TR-GAD:
At screening, current medications will be recorded (dose and frequency) and a medications log will also be completed at the 6 and 12 month follow up visits, if there are any changes to the medications recorded at screening. This information will be collected via participants' self-reports or extracted from GP medical records, with participants' consent. Participants in the intervention arm will be asked to refrain from engaging in other forms of psychotherapy during the delivery of the intervention, as per standard NHS practice, 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 within the CRF at 6 and 12 months, along with any interventions that participants are referred for after receiving the intervention.

6.4 Unblinding

It is not anticipated that an outcome assessor will need to know the treatment allocation. However, if the situation arises, site staff should discuss this with the UK Chief Investigator (CI) and Trial Manager. Any instances of unblinding will be documented within the CRF and be included as a secondary outcome for the trial. In the event of accidental unblinding, this will be recorded at 6 and 12 months, when the outcome assessors are asked to guess each participant's allocated group.

7. Assessments and procedures

7.1 Primary outcome measure

The primary outcome measure will be the Generalised Anxiety Disorder Assessment (GAD-7) (63). This is a 7-item self-report measure of GAD, which is routinely used with adults of all ages within primary and secondary care in the NHS. The GAD-7 will be completed at baseline (0 months), following confirmation of eligibility and consent, 6 months post-randomisation (the primary endpoint), and 12 months post-randomisation.

7.2 Secondary outcome measures

All secondary outcome measures will be completed at baseline (0 months), following confirmation of eligibility and consent, 6-month post-randomisation, and 12-month post-randomisation, with three exceptions. The Client Satisfaction Questionnaire-8 (64) will only be collected at 6-month follow-up. Adverse events will be collected at 6- and 12-month follow-up. Data on session attendance for those in the ACT arm will be collected after each session.

Secondary outcome measures will be as follows:
a) McGill Quality of Life Questionnaire-Revised (65): This is a self-report measure of quality of life that has good psychometric properties, and is sensitive to change. It comprises 14 items forming 4 subscales: Physical (3 items), Psychological (4 items), Existential (4 items) and Social (3 items). It is the preferred quality of life measure as the Existential subscale includes items consistent with an ACT approach (e.g. those in relation to a purposeful and meaningful life and achievement of life goals);
b) Geriatric Depression Scale-15 (66): A 15-item self-report measure of depression developed specifically for older people, necessary as GAD is frequently comorbid with depression;
c) Comprehensive Assessment of ACT processes (CompACT) (67): A 23-item self-report measure of psychological flexibility (akin to coping in conventional CBT), which ACT aims to develop. It has 3 subscales: openness to experience (which explores one's willingness to experience thoughts, emotions, sensations, etc), behavioural awareness (which assesses mindful awareness of one's actions), and valued action (which examines engagement in meaningful activities);
d) Health and social care resource use, including dose and frequency of prescribed medication (such as antidepressants, anxiolytics, benzodiazepines and other hypnotic drugs), over-the-counter medication (such as sedative antihistamines) and illicit substances: These data will be captured using a modified version of the Client Service Receipt Inventory (62), which is a measure of service utilisation;
e) EQ-5D-5L plus EQ-VAS (68): A 5-item self-report measure of health-related quality of life which will be used to calculate utility scores for quality-adjusted life years, and a visual analogue scale measure of health-related quality of life;
f) ICECAP-O (69): A 5-item self-report capability measure for older people which will be used to calculate capability-adjusted life years. The concurrent use of the EQ-5D-5L and ICECAP-O in older people is recommended in order to capture benefits to broader wellbeing than just health (70);
g) Adverse events (e.g. falls, new reports of suicidal ideation with or without active suicidal behaviours/plans, but without intent during the study [i.e. not reported at baseline], deaths, hospitalisations, etc). As falls are frequently under-reported, a question about falls will be added to the modified Client Service Receipt Inventory, where it will be linked to service use in order to identify significant/injurious falls;
h) Satisfaction with ACT and/or usual care will be assessed using the Client Satisfaction Questionnaire-8 (64). This will be assessed in both arms in order to avoid unblinding outcome assessors;
i) The Goal-Based Outcomes tool (71), a self-reported, idiographic outcome measure, will be used to assess personally meaningful behaviour change. This will ask a person to define 3 personally meaningful behavioural goals (with the emphasis on what they would like to be 'doing' rather than what they would like to be 'feeling'). They will then rate their progress towards this goal on an 11-point Likert scale (from 0 = not met at all to 10 = fully met). Assessing whether people are doing more in the presence of anxiety will permit examination of whether ACT is achieving its main aim of helping people to "live better" rather than "feel better";
j) Cognitive & Leisure Activity Scale (72): A 16-item self-report measure that assesses engagement in 16 types of activities, including cognitive, social, creative and spiritual activities;
k) Adherence (i.e. session attendance for those in the ACT arm).

7.3 Measures of bias

Expectations about treatment, participants' preferences for treatment, use of other forms of treatment during the trial and unblinding of outcome assessors are all potential sources of bias that can affect treatment outcomes. Consequently, the following measures of bias will be included:
i) *Expectations about treatment:* Prior to randomisation, all participants will be asked the following questions in relation to their expectations of treatment: "How much do you expect your symptoms to improve if you receive Acceptance and Commitment Therapy?" and "How much do you expect your life to improve if you receive Acceptance and Commitment Therapy?". They will be asked to rate these questions on a 5-point Likert scale from 0 (not at all) to 4 (completely);
ii) *Therapists' expectations about treatment:* After a participant's first therapy session, all therapists will be asked the following questions in relation to their expectations about treatment for the participant: "How much do you expect the participant's symptoms to improve after receiving Acceptance and Commitment Therapy?" and "How much do you expect the participant's life to improve after receiving Acceptance and Commitment Therapy?". They will be asked to rate these questions on a 5-point Likert scale from 0 (not at all) to 4 (completely);
iii) *Preferences for treatment:* Prior to randomisation, all participants will be asked the following questions in relation to their preferences for treatment: "Although you will be chosen at random to have either Acceptance and Commitment Therapy or usual care, if you could choose what treatment you received, how much would you hope

to receive Acceptance and Commitment Therapy?" and "How much would you hope to receive usual care (i.e. not Acceptance and Commitment Therapy)?". They will be asked to rate these questions on a 5-point scale from 0 (not at all) to 4 (completely);
iv) *Use of other forms of treatment:* A modified version of the Client Service Receipt Inventory (62) will be used to record other forms of psychological therapy and pharmacotherapy received outside of the study. Contamination in the control group (i.e. use of pharmacological or psychological therapies other than the study intervention) may attenuate the true effect of ACT. Consequently, additional exploratory data analysis to assess the impact of these therapies will be undertaken if used by a substantial proportion of participants;
v) *Unblinding of outcome assessors:* An assessment of blindness in blinded outcome assessors will be conducted at follow-up. Although participants will be asked not to reveal their allocation to outcome assessors, some may accidentally reveal this and some outcome assessors may be able to guess this. Therefore, outcome assessors will be asked to declare if they have been unblinded (and how). Those who have not been unblinded will be asked to guess whether they think participants were allocated to the intervention or control arm at follow-up.

7.4 Treatment fidelity

The NIH Behavioral Change Consortium's treatment fidelity framework (73) will be used to enhance treatment fidelity, as well as to guide assessment of this. A number of methods will enhance and/or monitor treatment fidelity. ACT training workshops will be delivered by the same core members of the trial team in order to ensure consistency of training sessions, and sessions will be videoed so that therapists can review them when needed. A treatment manual, developed in the FACTOID study, will be used to ensure consistency of ACT delivery. Group supervision via video call will be available on a weekly basis and will be provided by 4 core members of the trial team. This will be supplemented by an online supervisor-moderated forum in order to ensure that therapists can also access support at other times outside of supervision. The intervention has been specifically designed to meet the cognitive needs of older people with TR-GAD. Simplified worksheets (developed in the FACTOID study (15)), repetition of key concepts and a summary of the main points discussed in each session will be provided to participants in order to aid comprehension of ACT. Finally, ways in which participants can put ACT principles into practice in their daily lives and make personally meaningful behavioural changes will be explored and positively reinforced in each session.

Treatment fidelity will be assessed in a number of ways:
i) *Training:* Training workshops will be videoed and an independent ACT therapist will assess the fidelity of training to the ACT model. Any ACT inconsistent deviations will be recorded. Therapists' knowledge of ACT will be assessed through a clinical vignette-based written assessment at the end of training;
ii) *Treatment delivery:* All therapy sessions will be audio-recorded using an encrypted digital voice recorder, and 10% of randomly selected sessions will be rated on an ongoing basis throughout intervention delivery by an independent, experienced ACT therapist using the ACT Fidelity Measure (ACT-FM) (74). The ACT-FM is a 25-item measure, which assesses ACT fidelity in 4 domains (open response style, aware response style, engaged response style and therapist stance). Scores for each subscale are summed in order to produce a total ACT consistency score and a total ACT inconsistency score. Therapists will receive feedback on their rated sessions throughout the treatment delivery period. In addition, adherence to the treatment manual and therapy components will be measured using a checklist that therapists complete at the end of each session, which will be adapted from previous work (75);
iii) *Treatment receipt:* The Comprehensive Assessment of ACT processes (67) will be used to measure changes in psychological flexibility in older people with TR-GAD. Engagement with therapy will be defined by the number of sessions out of 14 attended: poor (0-3), moderate (4-6), good (7-10), excellent (11-14);
iv) *Treatment enactment:* An idiographic patient-reported outcome measure, the Goal-Based Outcomes tool (71), will be used to assess personally meaningful behavioural changes (see secondary outcome measures).

7.5 Screening and collection of sociodemographic and clinical data

For older people:
Potential participants will be asked to provide fully informed consent prior to data collection.

Socio-demographic and clinical data will be collected at screening in order to determine eligibility. This will include: i) age; ii) GAD diagnosis using the Mini-International Neuropsychiatric Interview (39); iii) current and previous treatment for GAD; iv) suicidal ideation, intent and plans using the Columbia-Suicide Severity Rating Scale Screener (40); and v) diagnosis of an imminently life-limiting illness, dementia or intellectual disability. In

addition, the Standardised Mini-Mental State Examination (76), a brief 30-item cognitive screening tool, will be used to assess global cognitive functioning. If potential participants score <25 out of 30 on the tool then the researcher will be invited to discuss this with the local PI or academic clinicians in the Trial Management Group as this may indicate cognitive impairment, but it may also be due to other reasons (e.g. translation issues if delivered through an interpreter).

The following baseline socio-demographic and clinical data will be collected for those who meet eligibility criteria and provide consent: i) data on protected characteristics including self-identified gender, ethnicity, marital and civil partnership status, sexual orientation, religion or belief, and disability in order to monitor the diversity of the sample (and make adjustments to recruitment strategies, where necessary); ii) living in urban/rural location, primary language and socioeconomic status; iii) highest level of educational qualification and current occupational status (paid or voluntary); iv) age of onset of GAD and number of previous episodes; v) comorbid psychiatric diagnoses using the Mini-International Neuropsychiatric Interview (39); vi) possible comorbid personality disorder on the Iowa Personality Disorder Screen (77); and vii) current/chronic illnesses using the Cumulative Illness Rating Scale-Geriatrics (78).

For therapists:
Participants will be asked to provide fully informed consent prior to data collection. Socio-demographic data collected at screening will include age and study therapist status. Additional socio-demographic data collected for all those study therapists who meet eligibility criteria and provide consent will include: self-identified gender, ethnicity, highest level of educational qualification, current occupation, number of years since qualifying as a therapist, and number of years practicing ACT.

7.6 Subsequent assessments and procedures

Data collection will be conducted in person (at home or in clinic) or via video call, phone, online via Qualtrics or post at 0 months, 6 months post-randomisation (+/- 6 weeks) and 12 months post-randomisation (+/- 6 weeks) by a blind outcome assessor from the research site or central research team, with the exception of the question about psychological therapies received on the adapted Client Service Receipt Inventory (62). All outcome measures completed by post will be returned in a pre-paid envelope. In order to prevent any potential unblinding of outcome assessors, the question about psychological therapies received on the adapted Client Service Receipt Inventory (62) will be administered in one of four ways: i) via post and then returned to the central study team at 6 months in a pre-paid envelope; ii) by online methods; iii) by telephone by the non-blind assessor arranging the follow-up visit; or iv) at the end of the outcome assessment session at 12 months, after the outcome assessor has completed the unblinding question. Participants who complete data collection via video call or phone will receive a copy of the screening and outcome measures via email or post in order to reduce working memory load and compensate for potential hearing difficulties when being asked questions. Mode of administration will be recorded at each time point as this may impact on the collection of some outcome measures.

Table 1 provides details of the data to be collected at each visit. The primary outcome measure for older people with TR-GAD will be the GAD-7 (63), with the primary endpoint being at 6 months post-randomisation. Further assessment at 12 months will examine whether potential gains are maintained at short-term follow-up. A summary of the participant timeline is outlined in Figure 1.

Table 1. Assessment intervals for measures used in the RCT.

Primary and secondary outcome measures and measures of bias (for older people with TR-GAD unless otherwise indicated)	**0 months**	**6 months**	**12 months**
Primary outcome measure			
Generalised Anxiety Disorder Assessment (GAD-7) (63)	✓	✓	✓
Secondary outcome measures			
McGill Quality of Life Questionnaire-Revised (65)	✓	✓	✓
Geriatric Depression Scale-15 (66)	✓	✓	✓
Comprehensive Assessment of ACT processes (CompACT) (67)	✓	✓	✓
EQ-5D-5L plus EQ-VAS (68)	✓	✓	✓

Quality-adjusted life years	✓	✓	✓
ICECAP-O (69)	✓	✓	✓
Capability-adjusted life years	✓	✓	✓
Goal-Based Outcomes tool (71)	✓	✓	✓
Cognitive & Leisure Activity Scale (72)	✓	✓	✓
Adverse events		✓	✓
Client Satisfaction Questionnaire-8 (64)		✓	
Adherence (session attendance in the intervention arm only)	After each session		
Cost-effectiveness-related measure			
Modified version of the Client Service Receipt Inventory (62)	✓	✓	✓
Measures of bias			
Treatment expectation[a]	✓		
Treatment preference[a]	✓		
Assessment of blindness (for outcome assessors only)		✓	✓
Measures of treatment fidelity			
ACT Fidelity Measure (ACT-FM) (74) (for ACT independent rater - intervention arm only)[b]	Duration of intervention delivery		
ACT checklist (for therapists only)[c]	After each session		

Notes: [a] This will be completed after consent, but prior to randomisation, after participants are given a rationale for ACT. [b] 10% of randomly selected sessions will be rated on a regular basis throughout the duration of intervention delivery, as stipulated by the random order of sessions to be rated, so that therapists can receive ongoing feedback on their intervention delivery. [c] An ACT checklist will be used to measure adherence to the treatment manual and therapy components.

7.7 Qualitative data collection

Older people with TR-GAD will be invited to complete one of two anonymous qualitative satisfaction questionnaires during the 6-month follow-up via post, email or online via Qualtrics. These will comprise a combination of open and closed questions, and there will be separate versions for the intervention arm and usual care arm. All older people with TR-GAD will be asked to complete qualitative satisfaction questionnaires in order to ensure that independent blind outcome assessors remain masked as much as possible. Those in the intervention arm will be asked questions in relation to the acceptability of ACT and its suitability and relevance to older people with TR-GAD, perceived benefits and limitations of the intervention, perceived mechanisms of impact, facilitators of and barriers to implementing the intervention in their everyday lives (including ease of understanding via translators and issues with translation, where applicable), and recommendations for revising the intervention. Those in the usual care arm will be asked questions in relation to the psychological aspects of their usual care. Questions will focus on what kind of formal and informal psychological support they received (if any), what was helpful and what was not, and what they felt would have been helpful.

If participants are unable to complete the written questionnaire (either via post, email or online), they will be invited to complete the questionnaire verbally via telephone, videoconference, or face-to-face interview. An independent member of the local or central research team will complete satisfaction questionnaires verbally with all those who cannot complete the written questionnaire. This will be recorded on an encrypted digital voice recorder (see section 11.3). This will ensure that independent blind outcome assessors remain masked as much as possible. The independent member of the research team will audio record any satisfaction questionnaires completed verbally using an encrypted digital voice recorder. Audio files will be uploaded to a secure server using a system called Data Safe Haven, which satisfies the highest level of security requirements of NHS trusts. The audio recordings will then be transferred and stored onto UCL's password protected secure electronic network. All data on encrypted digital voice recorders will be deleted after the data have been transferred. Data will not be transferred to any party not identified in this protocol and will not be processed and/or transferred other than in accordance with participants' consent.

All study therapists will be invited to complete an anonymous qualitative satisfaction questionnaire at the end of delivering ACT in the trial. This will explore how ACT was delivered in practice (e.g. treatment fidelity, ease of

delivering ACT, difficulty of skills for participants to learn, etc), facilitators of and barriers to implementing the intervention in the NHS (including ease of delivery via translators and issues with translation, where applicable), and recommendations for revising the intervention.

7.8 Discontinuation/withdrawal of participants

Discontinuation/withdrawal of participants will be managed in accordance with the Sheffield CTRU Participant Discontinuation and Withdrawal of Consent SOP. In consenting to participate in the trial, older people with TR-GAD are consenting to receive the intervention (if allocated), screening and outcome assessments at baseline and follow-up, and data collection. Participants will be made aware that their participation is voluntary and that they may discontinue from the trial, should they wish, at any time.

Excessive participant withdrawal from trial follow-up has a negative impact on the results of a study. A member of the local or central research team will explain the importance of remaining in trial follow-up to participants, and that changes to planned treatment need not imply withdrawal from the trial. Nevertheless, if participants do not wish to remain in the trial, their decision will be respected.

Participants will have the following options if they wish to withdraw:

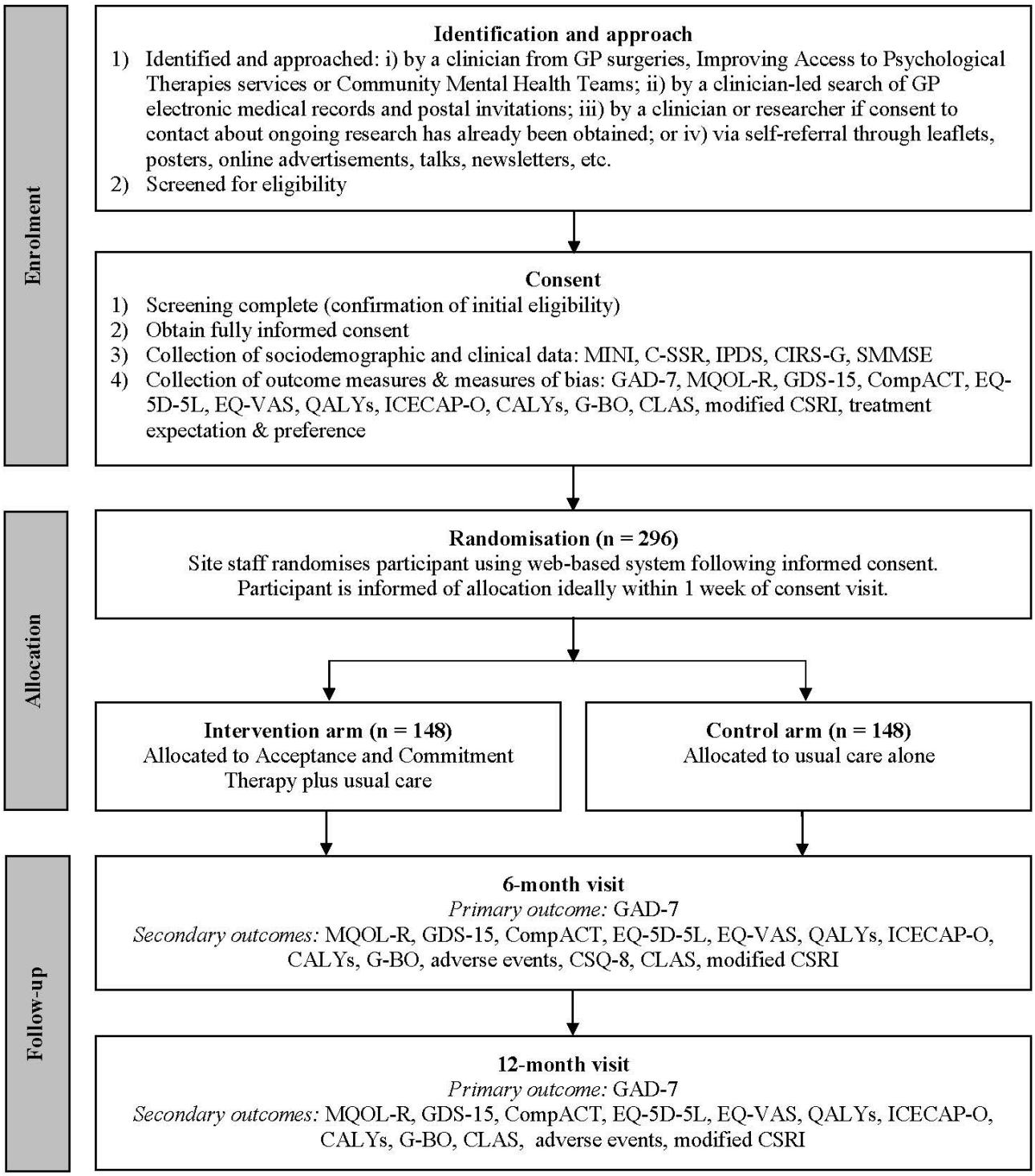
1. Withdrawal from the trial intervention (if allocated to the treatment arm), but not subsequent data collection (i.e. the participant would be withdrawn from therapy sessions only but would remain in the trial);
2. Withdrawal from the trial entirely (i.e. the participant would be withdrawn from both therapy sessions and subsequent data collection if allocated to the treatment arm or subsequent data collection alone if allocated to the control arm). Any data collected up to this point would be retained and used in the analysis. No further contact with regards to the trial would be made, aside from dissemination of trial results if the participant consents to this on their consent form. If the participant specifically requests for all their data to be removed, information regarding the participant would be retained at site, as part of the patient notes, along with their withdrawal form and request to delete the data. If this occurs, a Sheffield CTRU Data Evaluation SOP will be followed. The Statistical Analysis Plan (SAP) will provide details on how data are to be included/excluded from the statistical analyses.

If a participant requests to withdraw, they will be able to speak to a member of the local or central research team. This will be documented on a participant withdrawal form, within the Case Report Form. A participant may be withdrawn from the trial whenever continued participation is no longer in the participant's best interests, but the reasons for doing so will be recorded (wherever possible). Reasons for discontinuing the trial may include:

- Major escalation of mental health service support;
- Suicidal ideation with active suicidal behaviours/plans and intent, where the intervention is believed to be contributing to further distress;
- Illness or death that may exclude the possibility of engagement in the intervention;
- A person withdrawing consent or losing the capacity to consent to participate in the trial.

A participant will be classed as complete if they have continued in the trial until the last protocol defined visit. However, there may be missing visits and/or data. A participant will be classed as lost to follow-up if the participant has not completed the trial (i.e. completed their 12-month follow-up), despite attempts for further contact having been made.

Figure 1. Timeline for older people with TR-GAD in the RCT.



Notes: MINI = Mini-International Neuropsychiatric Interview, C-SSR = Columbia-Suicide Severity Rating Scale Screener , IPDS = Iowa Personality Disorder Screen, CIRS-G = Cumulative Illness Rating Scale-Geriatrics, SMMSE = Standardised Mini-Mental State Examination, GAD-7 = Generalised Anxiety Disorder Assessment, MQOL-R = McGill Quality of Life Questionnaire-Revised, GDS-15 = Geriatric Depression Scale-15, CompACT = Comprehensive Assessment of ACT processes, EQ-5D-5L = EuroQol-5 domains-5 levels, EQ-VAS = EuroQol visual analogue scale, QALYs = Quality-adjusted life years, ICECAP-O = ICEpop capability measure for older people, CALYs = Capability-adjusted life years, G-BO = Goal-Based Outcomes tool, CSRI = Client Service Receipt Inventory, CSQ-8 = Client Satisfaction Questionnaire-8, CLAS = Cognitive & Leisure Activity Scale.

7.9 Definition of end of study

The expected duration of the study is 39 months. The start of the study is defined as the date of recruitment of the first older person with TR-GAD to the trial. The end of the study is defined as the date of the last follow-up visit of the last older person with TR-GAD in the trial.

8. Recording and reporting of adverse events

Trial sites are to report Adverse Events (AEs) and Serious Adverse Events (SAEs) in conjunction with the Sheffield CTRU Adverse Events and Serious Adverse Events SOP.

8.1 Adverse events

An AE is any untoward medical occurrence in an older person with TR-GAD who is participating in the CONTACT-GAD trial. Incidents of AEs will be collected and recorded within the CRF. If suicidal ideation without active suicidal behaviours/plans and intent is identified, this will be recorded as an AE and the participant's GP (or equivalent healthcare provider in Australia) will be informed and the participant will be monitored weekly during therapy sessions (if in the ACT arm). Local standard clinical procedures will be followed for those in the usual care arm.

AEs will be categorised as follows:

- Any new co-morbid psychiatric condition reported;
- Any reported event that has significantly affected the psychological health status of the participant (e.g. a stressful life event such as a bereavement);
- New reports of suicidal ideation with or without active suicidal behaviour/plans, but without intent during the study (i.e. not reported at baseline);
- Other.

8.2 Serious adverse events (SAEs)

The definition of an SAE in relation to an older person with TR-GAD who is participating in the CONTACT-GAD trial is as follows:

- New reports of suicidal ideation with active suicidal behaviour/plans and intent;
- Reports of physical self-harm;
- Requires unplanned in-patient hospitalisation[a];
- Requires prolongation of existing hospitalisation[a];
- Is life-threatening[b];
- Results in persistent or significant disability or incapacity;
- Results in death;
- Considered medically significant by the investigator.

[a] Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation.
[b] A 'life-threatening' event refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

All of the SAEs defined above will be classified as unexpected.

Intensity
The following categories will be used to define the intensity of an SAE:

Category	Definition
Mild	The event does not interfere with the participant's daily routine, and does not require further procedure; it causes slight discomfort.
Moderate	The event interferes with some aspects of the participant's routine, or requires further procedure, but is not damaging to health; it causes moderate discomfort.
Severe	The event results in alteration, discomfort or disability which is clearly damaging to health.

Relationship to trial intervention
The relationship to the trial intervention will be categorised as follows:
i) reasonable possibility of being related;
ii) no reasonable possibility of being related;
iii) not assessable.

The assessment of causality must be made by a trained clinician, usually the PI or a Co-Investigator. If a causality assessment is not provided by the site or causality is recorded as 'not assessable', the event should be deemed to be related until the investigator confirms otherwise. If there is disagreement between the PI and UK CI over the causality assessment, the UK CI's decision will be final. Advice may be sought from the TSC if appropriate.

8.3 Reporting

AEs and SAEs can be reported for older people with TR-GAD at any stage of their trial participation. A member of the site team or central research team will also ask participants to self-report any AEs/SAEs at 6-month and 12-month follow-up visits. Therapists, clinicians or researchers will notify the local PI in the site team and/or un-blind members of research team if they become aware of any AEs/SAEs during the study. AEs will be recorded on the AE section of the paper CRF, and must be entered onto the electronic trial database within 1 week of completing the paper form. The events will be assessed by the local PI and the form will be stored within the CRF.

All SAEs must be reported to Sheffield CTRU and the sponsor within 24 hours of discovery at site. The following steps must be taken:

1. The event details need to be completed on the SAE form within the CRF;
2. The completed form needs to be downloaded and emailed to the following groups:
   - sponsor.noclor@nhs.net;
   - contact-gad-centralteam-group@sheffield.ac.uk;
   - ctru-saes-group@sheffield.ac.uk.

All SAEs that are deemed both "unexpected" and "related" to the intervention (ACT) or trial require expedited reporting. These must be reported to the REC within 15 days of being reported to the study team; this is the responsibility of the Sheffield CTRU. All SAEs will be reported in the periodic safety reports to the REC, Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC).

The Australian research team and Australian CI will follow the same procedures as described in the section above. In addition, the Australian research team will report local SAEs (i.e. for Australian-recruited participants) to their Research Governance Office (RGO) within 72-hours, in line with the National Health Medical Research Centre (NHMRC) requirements.

8.4 Risks

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

Suicidal ideation: Participants will remain under the care of their GP/consultant psychiatrist/care coordinator (or equivalent healthcare provider in Australia) for the duration of their involvement in the trial, where local SOPs will be followed. Risk of harm to self or others will be monitored throughout the trial using the Columbia-Suicide Severity Rating Scale Screener (40). If suicidal ideation without active suicidal behaviours/plans and intent is

expressed at any point then the participant's GP/consultant psychiatrist/care coordinator (or equivalent healthcare provider in Australia) will be contacted and the participant will continue to be monitored weekly (if in the ACT arm). Local standard clinical procedures will be followed for those in the usual care arm. If suicidal ideation with active suicidal behaviours/plans and intent is expressed at any point then the participant's GP/consultant psychiatrist/care coordinator (or equivalent healthcare provider in Australia) 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 will be made in full discussion with the participant, clinical team and Trial Management Group/DMEC (where necessary).

Inadequate treatment response: If a participant with TR-GAD remains moderately to severely anxious or depressed at the end of the final follow-up assessment (as indicated by a score of >8 on the GDS or a score of >10 on the GAD-7) then this will be discussed with the participant and their GP/consultant psychiatrist/care coordinator (or equivalent healthcare provider in Australia).

Confidentiality: 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 PIS. If there are any unexpected disclosures of actual or potentially illegal behaviour at any point during the trial then this will be discussed with the person disclosing the information, and the participant's GP/consultant psychiatrist/care coordinator (or equivalent healthcare provider in Australia) will be contacted (if necessary) and/or relevant authorities notified (if necessary). Local standard clinical procedures will be followed for safeguarding participants.

Potential distress: Evidence of any adverse effects from the ACT intervention will be monitored throughout the trial. Reasons for withdrawing participants with TR-GAD from the ACT intervention are listed in section 7.8. Reasons for withdrawing participants will be monitored by the Trial Management Group and DMEC throughout the duration of the study. Anyone experiencing an increase in distress will be assessed for risk, and local standard operating procedures will ensure safety is respected. New reports of suicidal ideation with active suicidal behaviours/plans and intent during the ACT intervention will be reported as Serious Adverse Events.

Lone working: All staff seeing participants in their own homes (e.g. therapists, members of the research team) 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.

8.5 Notifications of reportable protocol non-compliance

A non-compliance is a departure from the protocol or GCP that has been identified retrospectively.

A “serious breach” is a breach, of either the conditions and principles of GCP in connection with the trial; or the protocol relating to the trial, which is likely to affect to a significant degree:
(a) The safety or physical or mental integrity of the subjects in the trial; or
(b) The scientific value of the trial.

A very serious non-compliance significantly affecting either of the above may alone constitute a serious breach. Less serious but persistent, systematic or deliberate non-compliances might also be considered a serious breach. The sponsor will be notified immediately of any case where the above serious breach definition applies during the trial conduct phase. The UK CI or designated individual will notify the sponsor of any protocol non-compliance, within one week of becoming aware of the event.

8.6 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:
i) It is an accident or other incident which results in injury or ill health.
ii) It is contrary to specified or expected standard of patient care or service.
iii) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
iv) It puts the relevant Trust in an adverse position with potential loss of reputation.
v) It puts relevant Trust property or assets in an adverse position or at risk.

Incidents and near misses will be reported to the relevant Trust through DATIX as soon as the individual becomes aware of them.

8.7 Auditing

The sponsor will permit monitoring and audits by the relevant authorities, including the REC. The PI will also allow monitoring and audits by these bodies and the sponsor, and they will provide direct access to source data and documents.

9. Statistics

9.1 Planned recruitment rate

It is estimated that 650 potential participants in 27 months across a minimum of 15 sites will need to be identified and approached in order to consent and recruit 296 older people with TR-GAD. In order to meet the recruitment target, the identification rate will need to be 24.07 potential participants per month (1.60 per site per month), and the recruitment rate will need to be 10.96 potential participants per month (0.73 per site per month). Although this recruitment rate might seem low given that GAD is the most common anxiety disorder in older people with an estimated prevalence of 1-11% (1), GAD is commonly under-recognised and undertreated due to overlap in symptoms with other diagnostic categories (46,79–81). Many older people who meet diagnostic criteria for GAD are referred to primary and secondary care services with a diagnosis of major depression and comorbid anxiety or mixed anxiety and depression rather than GAD. Thus, underdiagnosis of GAD will be addressed in discussions with referrers.

The UK CI, the trial manager and research assistant (and Australian CI and research assistant where applicable) will maintain regular contact with recruiting sites via site visits, email, video call and telephone to ensure that recruitment targets are met and any issues with recruitment are managed promptly. “Trial champions” will be identified at each of the sites so that knowledge and processes about the trial are disseminated to all clinicians likely to be involved, and not just the senior PI at each site. A PI and Staff group comprising PIs and research staff from each recruitment site will meet on a monthly basis via video call in order to discuss successful recruitment strategies and any recruitment issues.

9.2 Stop/go criteria

A 9-month internal pilot in months 10-18 will use criteria outlined in Table 2 to determine progression to the full RCT. Success criteria for the overall trial will be: i) Recruitment to target (N=296); ii) ≥70% uptake of the intervention; and iii) Retention of ≥80% of participants for the primary outcome measure at the primary timepoint.

Table 2. Stop/go criteria for progression to the full RCT.

Progression criteria	**Red:** <50%	**Amber:** 50%-99%	**Green:** 100%
1. Trial recruitment % complete	<17% of total	17-32% of total	33% of total
2. Recruitment rate/site/month	<0.37/site/month	0.37-0.72/site/month	0.73/site/month
3. No. of sites opened	≤6	7-14	15
4. Total no. of participants recruited	<50	50-98	99
5. Completion of 7/14 sessions	<50%	50-99%	100%
6. % of sessions rated with a total ACT inconsistency score of <18 on the ACT Fidelity Measure	<50%	50-99%	100%

9.2 Sample size calculation

Previous research has reported that improvements of 3-4 GAD-7 units are regarded as clinically important changes to individual patients (82–85). Smaller differences would expect to be seen at a population level since not every person responds to therapy. The following sample size is therefore based on a change of approximately 2 GAD-7 units (0.4 SD) which, based on Normal distributional theory, would mean an additional 15% of people having a clinically important improvement of 3 units compared with usual care. This is similar to the 0.40-0.46 SD difference observed in systematic reviews of ACT for mental and physical health conditions and CBT for GAD (20,86). Additionally, the effect size has been reduced from 0.4 to 0.37 SD as this will include people with limited or no spoken English necessitating the use of an interpreter, who may therefore not engage as well with talking therapies.

An individually randomised trial would require 108 participants per arm to achieve 90% power to detect a 0.37 SD difference at the 5% level, assuming a correlation of 0.55 between scores at 0- and 6-months, as seen in our

previous feasibility study (15,16). Incorporating an anticipated loss to follow-up of 20% at 6-months (based on our previous feasibility study (15,16)) and an intraclass correlation coefficient (ICC) of 5% among 30 therapists in the intervention arm, similar to previous studies (87), increases this to 156 intervention and 135 control participants (88). In order to maintain a 1:1 allocation, this has been modified to 148 participants per arm (296 participants in total), which is sufficient to maintain 90% power.

9.3 Quantitative analysis

The primary outcome measure will be analysed using multi-level modelling in which treatment group and baseline score will be included as fixed effect covariates and therapist will be included as a random effect to account for potential clustering. Analyses will be conducted separately at 6 months (the primary analysis timepoint) and 12 months. The difference between groups in mean GAD-7 total score will be quantified by the model coefficient, along with its 95% confidence interval. Primary analyses will be by intention to treat, but additional sensitivity analyses will assess the impact of session uptake using complier-average causal effect (CACE) analyses to model the average treatment effect among those who were considered "compliant" with ACT. For the purpose of trial data analysis, completion of seven sessions will be regarded as a minimum number allowable for an adequate exposure to treatment in the protocol, with participants that receive fewer than seven sessions being a deviation from this. As the minimum dose can vary across participants, this will be assessed further using a CACE analysis in which treatment outcome will be examined in relation to the number of sessions received. In addition, sensitivity analyses will examine the consistency of outcomes across sites, baseline GAD severity, age at first onset and baseline psychotropic medication use. Age at first onset is included here as a bimodal distribution of age of onset was found in the FACTOID feasibility study (15,16): 35% of participants reported experiencing difficulties for the past 1-5 years, while another 35% reported experiencing difficulties for over 30 years. Similar findings have been reported in other studies of GAD in working age adults and older people (89–91). Furthermore, higher rates of psychiatric comorbidity, psychotropic medication use and severe worry have been reported among older people with GAD with an early compared to late onset of symptoms (i.e. before vs. after 50 years of age) (89), all of which may impact on treatment outcome. Secondary outcome measures will be analysed in a similar fashion to the primary outcome measure.

Additional exploratory analyses will be undertaken to assess the consistency of treatment effects across the following subgroups: i) patient preference for treatment; ii) expectations with respect to treatment; iii) comorbid depression (or cothymia); iv) meeting screening criteria for a personality disorder; v) presence of a major life event that precipitated GAD; vi) limited or no spoken English skills; vii) country of recruitment; viii) mode of therapy delivery (in-person vs. remote delivery); and ix) type of treatment resistance (pharmacotherapy, psychotherapy or both). The justification for conducting exploratory analyses with respect to treatment preference, expectations and spoken English skills is discussed elsewhere. The remaining subgroup analyses are suggested as it has previously been argued that the GAD diagnostic category should be abandoned and replaced with one of three possible diagnoses (79): i) mixed anxiety-depression due to the fact that these symptoms commonly occur together, so-called cothymia (92); ii) 'general neurotic syndrome' or 'general nervous syndrome' due to the overlap between personality status and GAD; and iii) an adjustment disorder due to experiencing a major life event (i.e. life event-precipitated GAD). Additionally, it was suggested in the FACTOID study (16) that an examination of these characteristics, as well as treatment response, should be explored further in a larger-scale study. Finally, the impact of contamination (e.g. psychological therapy in the control arm) will be assessed in a per-protocol analysis (93).

It is expected that some participants will have missing outcome data either due to death, loss to follow up or withdrawal from the study. The number of missing values will be summarised by treatment group, time point and reason. Multiple imputation using Rubin's rules (94) will be implemented for the primary endpoint.

Adverse events will be summarised as the number and percentage of patients experiencing each event and the number of events by treatment arm.

9.4 Qualitative analysis

Qualitative data from open-ended questions in the satisfaction questionnaire will be transcribed verbatim and anonymised to maintain confidentiality. Data will then be analysed iteratively using a focussed thematic analysis (95,96). Two members of the research team will independently code initial questionnaires using the computer programme, NVivo, before constructing an analytical framework around: i) the acceptability, suitability, relevance, perceived benefits and limitations, perceived mechanisms of impact, and facilitators of and barriers to implementation of ACT for older people with TR-GAD for those in the intervention arm; and ii) the psychological

support received, what was felt was needed, and the helpfulness of psychological support for those in the usual care arm. The analytical framework will be applied to the remaining questionnaires, with themes and subthemes refined as necessary. Ideas about themes and relationships will be discussed with the Public Involvement Group. Findings will be used to make further refinements to the intervention, particularly with respect to implementation in clinical practice.

9.5 Informal mixed-methods process analysis

Quantitative data will be analysed as follows:
1) Intervention uptake: Data collected on number of sessions attended, modality of sessions, use of interpreters and reasons for non-attendance will be analysed to explore what contextual factors (such as participant sociodemographic and clinical characteristics at baseline) may influence uptake of the intervention;
2) Treatment fidelity: Data collected on Total ACT consistency and inconsistency scores from the ACT Fidelity Measure (74) will be analysed to explore what contextual factors (such as therapist characteristics at baseline and mode of delivery) may influence treatment fidelity;
3) Reach: Sociodemographic data from the trial will be analysed to explore reach and uptake in eligible populations in diverse settings and identify any under-represented populations through comparison with Office of National Statistics area level census data;
4) Outcomes: As outlined above, sensitivity analyses and additional exploratory analyses will identify what contextual factors (such as clinical characteristics at baseline) are associated with variations in primary and secondary outcome data.

9.6 Economic evaluation

A within trial cost-utility analysis will present the incremental costs per quality-adjusted life year gained of older people with TR-GAD receiving tailored ACT plus usual care vs. usual care alone from an NHS and social care perspective. Costs will be estimated for each participant and will include costs for delivering the intervention (e.g. staff time for delivering the intervention, cost of materials and cost of training staff to deliver the intervention, and mode of therapy delivery). Data on health and social care resource use will be collected using the modified Client Service Receipt Inventory (62). This will include primary and secondary health and social care usage such as medications, physiotherapy, GP and hospital visits, day care services and social community care services (such as home help for household tasks and/or personal care and social workers). Unit costs will be derived from appropriate national sources and will include NHS reference costs and Personal Social Service Research Unit costs (97,98). The standard version of the EQ-5D-5L (68) will be used to collect patient reported health status. Values for EQ-5D-5L for England will be used based on NICE advice at the time of analysis, which may either be to use the value set currently in collection or a mapping approach. These will be calculated using the area under the curve method. Where data on the EQ-5D-5L or resource use are missing, multiple imputation techniques in line with those described above will be implemented. Differences between costs and quality-adjusted life years in the two groups will be described and the incremental cost effectiveness ratio, with associated uncertainty, will be calculated. Clinical effectiveness data will be used to judge whether there is evidence of continued benefit from the treatment at 12 months and any evidence of a waning of effect. This will determine if there are grounds to extrapolate the analysis beyond the 12 months observed period using a simple decision model to estimate costs and benefits. This may be important since continued health benefits are unlikely to be matched by increased costs, given the upfront costs of providing the intervention. The time period for the model or appropriate methods for extrapolation cannot be determined at this stage. Any model based extrapolation will adhere to standard methods to reflect uncertainty including probabilistic sensitivity analysis and one-way/multi-way analyses. A separate analysis of over-the-counter medication will also be conducted in order to assess whether there are significant differences between treatment arms. A sensitivity analysis including these costs will be conducted if differences are non-negligible. Similar analyses will be conducted for capability-adjusted life years from the ICECAP-O (69).

With respect to the pooling of UK and Australian data, the base case analysis will pool data on both outcomes and resource use from all participating sites in the UK and Australia as usual care and health systems are considered to be similar in both countries and resource use is expected to be comparable. UK-specific unit costs and UK/England EQ-5D index scores will be applied to the participant level data and the analysis will proceed on the full dataset, maximising use of the trial data. Multilevel modelling of costs and outcomes will be used in a sensitivity analysis, to explore the potential impact of clustering at the national and/or therapist level. An exploratory analysis of treatment effect will be conducted by country of recruitment.

10. Trial supervision

10.1 Oversight

The study will be conducted in line with the Helsinki Declaration. Camden and Islington NHS Foundation Trust is the nominated sponsor. Research governance will be led by the Research and Development Organisation of the lead trust. The local PI will be responsible for the trial at each participating site and it will be registered and approved with each local Research and Development (R&D) department. The study will be conducted in accordance with the protocol, GCP and Sheffield CTRU SOPs. The three committees which will govern the conduct of the trial are:

- Trial Management Group (TMG)
- Trial Steering Committee (TSC)
- Data Monitoring and Ethics Committee (DMEC)

The TMG will comprise the UK CI, Australian CI, co-applicants, collaborators, and two interested members of the Public Involvement Group, and relevant trial staff. The TMG will meet in person/via video call at the beginning of the study to outline the development of the intervention, tasks involved, and target deadlines. Thereafter, the group will meet monthly, extending to every 2-3 months when recruitment is well established, to monitor progress and address issues and attainment of milestones. This group will set target deadlines, monitor the conduct and progress of the study, and troubleshoot any issues that arise. It will also review recruitment figures, incidents and substantial amendments to the protocol prior to submission to the REC. In addition, it will 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 TMG will send updates to the TSC and DMEC.

The TSC will include an independent Chair, an independent statistician, an independent health economist, an independent clinician, two independent Public Involvement representatives and the UK CI. The details of these members will be confirmed closer to the time of the study and may be subject to change during the course of the trial. The group will meet approximately every 6 months via video call to review progress and address any issues as necessary. Representatives of the sponsor and research network will also be invited to attend meetings. The role of the TSC is to provide supervision of the protocol and statistical analysis plan, to provide advice on and monitor the study, to review information from other sources and consider recommendations from the DMEC. The TSC will meet at regular intervals, as defined in the TSC terms of reference.

The DMEC will include an independent Chair, an independent statistician, and an independent clinician. The details of these members will be confirmed closer to the time of the study and may be subject to change during the course of the trial. The group will meet approximately every 6 to 12 months via video call, depending on the progress and stage of the tria at regular intervals, as defined in the DMEC charter. The role of the DMEC will be to discuss issues related to data collection, ethical issues and other incidents, and will provide recommendations in relation to data monitoring and ethical or safety issues, as necessary. It will be able to recommend premature closure of the study, if necessary.

10.2 Description of any interim analyses and stopping guidelines

There are no planned interim analyses or stopping rules based on efficacy. The trial may terminate prematurely if it fails to meet progression criteria following a 9-month internal pilot in months 10-18 of the RCT or on the basis of safety concerns.

11. Data handling and record keeping

11.1 Data management

The Sheffield CTRU will oversee data collection, management and analysis and ensure the trial is undertaken according to Good Clinical Practice Guidelines and CTRU SOPs. Data will be collected and retained in accordance with the UK's Data Protection Act (2018), which in turn comply with the Australian Privacy Principles (APP) set out in the Australian Privacy Act (1988).

Qualtrics may be used as digital option to collect consent and primary and secondary outcome measures (see section 7). Digital versions of the consent form and outcome measures will be sent via an online link to participants, managed by the central research team at the CTRU. Access to the Qualtrics system is restricted to individuals at the CTRU via a personalised login. Qualtrics servers are protected by high-end firewall systems and scans are

performed regularly by Qualtrics to ensure that any vulnerabilities are quickly found and patched. Qualtrics has obtained ISO 27001, ISO/IEC 27017, ISO/IEC 27018 and ISO 9001 security certifications: these are internationally recognised best practice frameworks for information security management systems.

Trial data will be entered on a study database hosted on the CTRU's web-based data management system (Prospect). Prospect stores all data in a PostgreSQL database on virtual servers hosted by Corporate Information and Computing Services (CiCS) at the University of Sheffield. Prospect uses industry standard techniques to provide security, including password authentication and encryption using Secure Sockets Layer (SSL) / Transport Layer Security (TLS) (i.e. encryption-based internet security protocols). Access to Prospect is controlled by usernames and passwords, and a comprehensive privilege management feature can be used to ensure that users have access to only the minimum amount of data required to complete their tasks. This will be used to restrict access to personal identifiable data. Australian participants will be asked to consent to their personal data and research data being transferred to and stored by the University of Sheffield, UK. This will also be disclosed in the PIS.

The research staff at sites will be responsible for data entry locally. A member of staff at each site will enter data from source documents into the trial specific Prospect database when available. Validation rules will be defined within Prospect, and automated validation reports will regularly check the data against these rules. The Sheffield CTRU trial manager, research assistant and the data management team will work with sites to ensure the quality of data provided. The trial manager, research assistant, data manager, PIs, any research nurses and site staff will be able to access the database via a web browser through the use of usernames and encrypted passwords. The system has a full electronic audit trail and is regularly backed up. The study database will incorporate quality control procedures to validate the trial data. Error reports will be generated where data clarification is needed. Output for analysis will be generated in a format and at intervals to be agreed between Sheffield CTRU and the UK CI. Study-specific procedures for data management will be detailed in a data management plan.

An equivalent process will be used in Australia to collate the trial data via Macquarie University, which will be shared with the University of Sheffield, UK.

11.2 Completing CRFs

All CRFs will be completed and signed by staff that are listed on the site staff delegation log and authorised by the UK CI/PI to perform this duty. The UK CI will be responsible for the accuracy of all data reported in the CRF. In line with Camden & Islington NHS Foundation Trust's (Sponsor) Data Protection Policy, UK study documentation and pseudonymised data will be securely kept for a period of 10 years following completion of the study. Australian study documentation and pseudonymised data stored in Australia will be securely kept for a period of 15 years following completion of the study.

11.3 Data handling

All data will be collected in accordance with the consent forms and information sheets for older people with TR-GAD and study therapists, and this protocol. Camden & Islington NHS Foundation Trust, as the study sponsor, and UCL, will act as the data controller for the study. All data will be handled in accordance with the UK's Data Protection Act (2018). Data management will be provided by the University of Sheffield CTRU who adhere to their own SOPs relating to all aspects of data management including data protection and archiving. A separate data management plan (DMP) will detail data management activities for the trial in accordance with the CTRU's Data Management Plan SOP

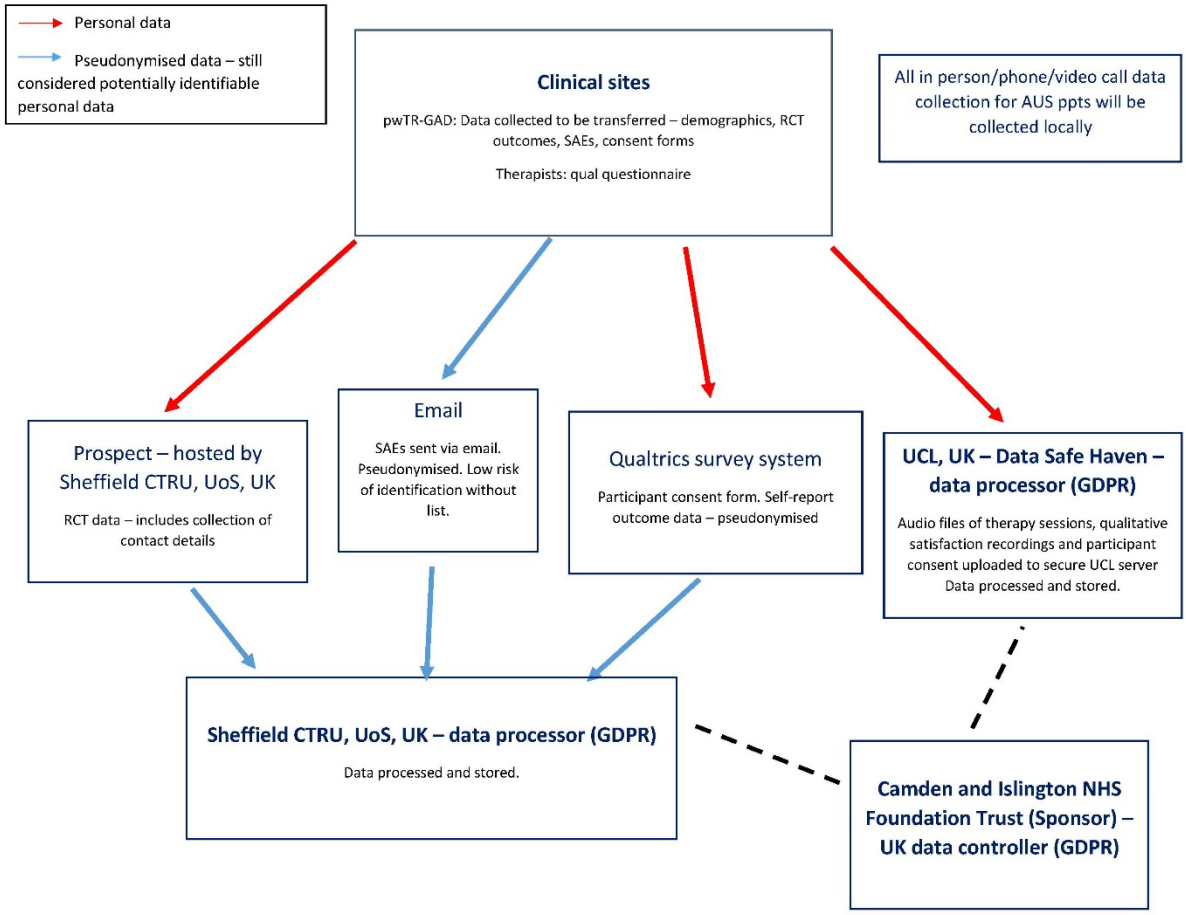
Participants will be assigned unique identification numbers. Prospect will store a participant's name, address, phone number and email address. Prospect's permissions system will be used to ensure that access to names and contact details will be restricted to those members of the study team who need to contact participants. All data will be held on a secure server with access restricted to the research team.

Audio files of therapy sessions and any Satisfaction questionnaires recorded on encrypted digital voice recorders will be uploaded to a secure server using UCL's system called Data Safe Haven (see Figure 2), which satisfies the highest-level security requirements of NHS trusts. Treatment integrity ratings will be completed by an independent ACT therapist who will blindly review audio files stored on the secure server via Data Safe Haven. (i.e. they will not know the names of therapists or participants), and will be asked to agree to maintaining confidentiality prior to rating sessions. Data will not be transferred to any party not identified in this protocol and will not be processed

and/or transferred other than in accordance with participants' consent. Australian participants will be asked to consent to audio files of their therapy sessions being transferred to and stored by University College London, UK. This will also be disclosed in the PIS.

In the UK, Sheffield CTRU will view copies of consent forms from older people with TR-GAD for monitoring purposes. Where monitoring is conducted remotely, the local research team will be requested to screen share a scanned copy of consent forms via secure videoconferencing. The video call will not be recorded and should take place in a room where no one other than the local and central research team can view the monitoring form. An equivalent process will be followed in Australia. Audio recordings of verbal consent obtained by telephone or videoconference will be uploaded to Data Safe Haven (see Figure 2). Any photocopies will be destroyed once scanned, and participant and therapist consent will be sought for sending copies of the consent forms and making audio recordings of verbal consent.

Figure 2. Trial Data Flow Diagram.



11.4 Confidentiality

Participant confidentiality will be respected at all times. All data will be handled in accordance with the UK's Data Protection Act (2018). The CRFs will not bear the participant's name or other personal identifiable data. The contact details form for older people with TR-GAD will be removed from the CRF once complete and stored in the investigator site file with the consent form. The participant's trial identification number will be used for identification and this will be clearly explained in the information sheets. All participant information will be stored in accordance with the UK's Data Protection Act (2018), with any personally identifiable information, stored in locked cabinets. 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. No identifiable Australian patient data will be shared with the UK team.

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 dementia, or other undiagnosed psychiatric conditions (e.g. clinically significant depression or anxiety), then the GP (or equivalent healthcare provider in Australia) of the older person with TR-GAD will be informed with the participant's consent (or without their consent if there are concerns about risk of harm to self). The GPs (or equivalent healthcare providers in Australia) of older people with TR-GAD will also be informed of their participation in the trial, with participants' consent.

11.5 Plans to promote participant retention and complete follow-up

Loss to follow-up and participant withdrawal will be minimised in a number of ways:

1. Older people with TR-GAD will be encouraged to discuss any difficulties they are having regarding attendance or engagement in the sessions with their therapists.
2. Participation in the trial will be assisted by the provision of funds towards travel for older people with TR-GAD to travel to clinic to receive therapy. Where applicable, a member of site staff will discuss funding for travel with the participant. There will also be provision of funds towards travel for therapists to travel to participants' homes, if required.
3. Older people with TR-GAD will be provided with flexible means of participating in therapy sessions, wherever possible (e.g., face-to-face at home or in the clinic, or via videoconference or telephone).
4. Older people with TR-GAD will be provided with flexible means of participating in outcome assessments, wherever possible (e.g. via telephone, videoconference, post, online, or face-to-face interview at home or in the clinic).
5. As participants who are hard of hearing may struggle with communication by telephone and video, in-person assessments and therapy sessions will be available, where possible, if preferred.
6. Evidence-based procedures for recruiting and maintaining study participation and encouraging participants to complete outcome measures will be adopted (e.g. the use of incentives such as non-contingent vouchers for completion of follow-up measures, contacting people prior to outcome assessments, sending greetings cards, personalizing letters, and maintaining contact through study newsletters and study branding (99)).
7. An online therapist peer support forum will be available to provide study therapists with the opportunity to receive additional support from those who are currently delivering the intervention. This will be in addition to group supervision via videoconference that therapists will be invited to attend on a fortnightly basis. The online forum will be set up on Google Groups and membership will be by invitation only.
8. “Trial champions” will be identified at each of the recruitment sites so that knowledge and processes about the trial, including ways of minimising loss to follow-up and withdrawal, are disseminated to all clinicians likely to be involved, and not just the senior PIs at each site.
9. Potential participants will be made aware, during screening, consent and in the PIS, of the importance of complete datasets and the impact that missing data has on a trial, as previously recommended (54). Prior to obtaining consent and entering the potential participant into the study, a member of the local or central research team will make it clear to the potential participant the number of follow-ups that will take place and the assessments that will be completed during these follow-ups. Where a potential participant expresses concern, the research team will talk through these concerns and explain why these assessments and/or visits will take place.

12. Data access and quality assurance

12.1 Data quality assurance

Prospect provides a full electronic audit trail, as well as validation features which will be used to monitor trial data quality, in line with CTRU SOPs and the Data Management Plan (DMP). Error reports will be generated where data clarification is required. Rates of missing data and data points which are out of the expected or allowed range will be presented to the team at monthly management group meetings.

12.2 Monitoring

The sponsor will determine the appropriate level and nature of monitoring required for the trial. The Sheffield CTRU SOPs 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 trial. A trial specific site monitoring plan will be established prior to the commencement of the trial. The trial will be monitored in accordance with the agreed plan.

12.3 Record keeping and archiving

Trial documents will be retained in a secure location during and after the trial has finished. Participating sites recognise that there is an obligation to archive trial-related documents at the end of the trial (as such end is defined within this protocol). All trial documents held in the CTRU will be archived and retained for 10 years from the end of the trial. All trial documents held at Macquarie University will be archived and retained for 15 years from the end of the 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. All archived documents will continue to be available for inspection by appropriate authorities upon request. Data held by the CTRU will be stored in accordance with the CTRU's Archiving SOP. Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for the period stated above.

13. PPI

Public involvement will occur in numerous ways throughout the trial in order to provide partnership and enhance the relevance, appropriateness and practicality of the intervention to older people with TR-GAD:
A Public Involvement Group comprising approximately 6-7 older people with lived experience of GAD will meet approximately every 6 months in the first 2 years of the study and annually thereafter via video call. A range of issues will be discussed in this group, including study progress, recruitment strategies, study materials, therapist training, interpretation of findings from qualitative satisfaction questionnaires, and dissemination of findings. Steps similar to those described for recruitment will be taken to ensure diversity in the membership of this group, including involving people without GAD who have awareness of cultural sensitivity issues.
ii) One to two interested members of the Public Involvement Group will be invited to join the TMG;
iii) Two independent older people with lived experience of GAD will be invited to join the TSC;
iv) Two interested members of the Public Involvement Group will be invited to participate in training of therapists (with training and support from the UK CI and PPI lead);
v) Interested members of the Public Involvement Group will be invited to participate in local and national presentations and/or co-write blogs for a public audience about key findings (with training and support from the UK CI and PPI lead).

14. Publication

14.1 Dissemination

Dissemination to the academic and clinical community, service users and the broader public will occur through:
i) Peer-reviewed, international open-access academic journals (e.g. The Lancet, Journal of the American Geriatrics Society, the International Journal of Geriatric Psychiatry). The protocol will be published and findings will be reported in accordance with reporting guidelines for protocols (SPIRIT) (100), non-pharmacological treatment interventions (CONSORT and TIDieR) (101,102), economic evaluations (CHEERS) (103) and qualitative research (COREQ) (104);
ii) Blogs about key findings co-written with the Public Involvement Advisory Group for a public audience;
iii) National and international academic conferences (e.g. Association of Contextual Behavioural Sciences Conference, World Congress of Behavioural and Cognitive Therapies);
iv) Local clinical conferences and meetings;
v) Talks to local groups, Primary Care Research Network, MIND and other organisations following guidance from the Public Involvement Advisory Group, and including an interested member of this group;
vi) University media releases, Twitter feeds and the University website;
vii) Training and seminars delivered via ACT special interest groups and professional bodies (such as the Association of Contextual Behavioural Sciences and the British Psychological Society's ACT and clinical health special interest groups), associated conferences and UK regional ACT clinician groups;
viii) Participants will be sent a summary of the findings once the trial has concluded - we will obtain consent for this when they enter the trial.

14.2 Publication policy

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

i) Conception and design, or analysis and interpretation of data;
ii) Drafting the article or revising it critically for important intellectual content;
iii) 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.

14.3 Intellectual property

All intellectual property rights and know-how in the protocol and in the results arising directly from the trial, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to Camden & Islington NHS Foundation Trust (Sponsor). Each participating site agrees that by giving approval to conduct the trial at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to the Sponsor and to disclose all such know-how to the Sponsor, with the understanding that they may use know-how gained during the trial in clinical services and teaching to the extent that such use does not result in disclosure of the Sponsor's confidential information or infringement of the Sponsor's IPR.

14.4 Projected outputs and impact

Projected outputs from this new psychological approach to the management of TR-GAD in older people will include: i) a tested intervention designed to meet the specific psychological, physical and cognitive needs of older people with TR-GAD in the NHS, refined using qualitative data from the RCT so that it is optimally tailored to this population; ii) establishment of definitive estimates of the clinical and cost effectiveness of ACT for older people with TR-GAD; and iii) an expert-designed, acceptable and efficient training program for training NHS clinicians in ACT that could be readily adapted to train clinicians working with other mental and physical health conditions. Ultimately, if clinical and/or cost effectiveness of this approach is demonstrated, timely and much needed evidence-based guidance will be provided to the NHS and other international bodies about the management of TR-GAD in older people.

One of the trial's objectives is to engage the public, stakeholders (including NICE, NHS England, NHS clinical commissioners and other policy makers) and mental health services in order to ensure readiness for implementation in clinical practice. This will be addressed by setting up an Implementation Working Group comprising members of these groups. If ACT plus usual care is found to be clinically and/or cost effective in older people with TR-GAD, the TMG will work with the Implementation Working Group to ensure that the intervention can be rolled out in clinical practice through existing primary and secondary care psychological therapies services. It is envisaged that ACT skills developed through working with older people with TR-GAD could be further cascaded to other clinical populations (e.g. working age adults with GAD), similar mental health conditions (e.g. health anxiety), and long-term physical health conditions (e.g. chronic pain).

15. Finance

There are no financial interests for the UK CI, Australian CI, Co-Investigators, or collaborators. It will also be ensured that there are no financial interests for the TSC or DMEC. The trial funding has been reviewed by a sponsor representative and deemed sufficient to cover the requirements of the trial. Research costs and service support costs will be supported via the sponsor and the Local Clinical Research Network, respectively. The research costs for the study have been funded by the NIHR HTA programme (NIHR134141; £1,527,258.19) and the NHMRC-NIHR Collaborative Research Grant Scheme (2014745; AUS $358,767.00).

16. Ethics approval

16.1 Ethical requirements

REC favourable opinion and ethical and research governance approvals through the HRA will be obtained prior to the trial commencing. Recruitment will not commence until full ethical and research governance approvals have been obtained. Research governance will be led by Camden and Islington NHS Foundation Trust (Sponsor). The Sponsor will ensure that the trial protocol, information sheets, consent forms, and submitted supporting documents have been approved by the appropriate REC (in the UK and Australia), prior to any participant recruitment. The protocol, and all other supporting documents including any 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 trial will be reviewed by the TSC and DMEC. The trial has been registered as an RCT and has been allocated an International Standard Randomised Controlled Trial ID

Number (ISRCTN ISRCTN85462326) and an Australian New Zealand Clinical Trials Registry ID number (ANZCTR [Insert once assigned]).

Amendments will not be implemented prior to receipt of the required approvals. Before any NHS site may be opened to recruit participants, the UK CI or designee must receive confirmation of capability and capacity in writing from the relevant Trust's Research & Development department. It is the responsibility of the UK CI or designee at each UK 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. Before any Australian site may be opened to recruit participants, [to be inserted].

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 UK CI will prepare the annual progress report. Within 90 days after the end of the trial, the UK CI/Sponsor will ensure that the main REC is notified that the study has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial. The UK CI 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. As the intervention is psychological, the study is not covered by the Medicines for Human Use (Clinical Trials) Regulations 2004.

17. Indemnity, compensation and insurance

The following UK indemnity processes will be followed:

1.) Design of the study - Where the protocol author is the substantive employee or holds an Honorary contract of an NHS organisation, then indemnity is provided for harm arising from the design of the study though NHS schemes. No proof of indemnity is expected.

2.) Management of the study - Where an NHS organisation is a sponsor (Camden & Islington NHS Foundation Trust), then indemnity is provided through NHS schemes. No proof of indemnity is expected for NHS sponsored research. If an NHS member of staff performs research activities in a non-NHS location, then NHS indemnity still applies.

3.) Conduct of the study- Where the research involves NHS patients under the care of NHS organisations, indemnity for harm to participants resulting from clinical negligence is provided through NHS indemnity schemes. No proof of indemnity is expected. Conduct will therefore be covered under a mix of indemnity schemes including the NHS, Clinical Negligence Scheme for General Practice (CNSGP), or equivalent for devolved nations, and independent professional indemnity schemes.

In the UK, participants recruited through an NHS trust will be eligible to exercise their rights under the NHS complaint policy. In addition, participants are able to contact the UK study team or CI regarding a complaint in the first instance. If participants feel their concern has not been handled in a satisfactory way, they can contact the Sponsor (sponsor.noclor@nhs.net).

Camden & Islington NHS Foundation Trust holds insurance against claims from UK participants for harm caused by their participation in this trial. UK participants may be able to claim compensation if they can prove that Camden & Islington NHS Foundation Trust has been negligent. Macquarie University holds insurance against claims from Australian participants for harm caused by their participation in this trial. Australian participants may be able to claim compensation if they can prove that Macquarie University has been negligent.

This trial has been funded by the NIHR HTA (project number: NIHR134141) in the UK. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. Components of the trial has been financed by the NHMRC (2014745) in Australia. Details have been drawn up in a separate agreement. If there is negligent harm to UK participants during the trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity will cover NHS staff, medical academic staff with honorary contracts and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

18. Declaration of interests

None declared.

19. References

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