The clinical and cost effectiveness of internet-delivered self-help Acceptance and Commitment Therapy for family carers of people with dementia (iACT4CARERS): A randomised controlled trial with ethnically diverse family carers

Statistical Analysis Plan

Version 1.0

19th June 2025

Authors and approvers	Title	Signature	Date
Naoko Kishita	Chief Investigator	Signed	19 June 2025
Mizanur Khondoker	Trial Statistician	Signed	22 June 2025
Ramesh Vishwakarma	Trial Statistician	Signed	19 June 2025
Emma Flanagan	Trial Manager	Signed	19 June 2025

SAP REVISION HISTORY

Document Name	Version No.	Effective Date
iACT4CARERS Statistical Analysis Plan	1.0	19/06/2025

Contents

1. Administrative Information

Sponsor:	University of East Anglia (UEA)
Sponsor Reference:	ID: R210595
Funder:	NIHR
Funder Reference:	National Institute for Health and Care Research Health Technology Assessment (HTA) Programme: NIHR150071
Trial Registration:	ISRCTN45995725
CTA:	n/a
IRAS:	324157
Chief Investigator:	Dr Naoko Kishita
Trial Statisticians:	Dr Mizanur Khondoker Dr Ramesh Vishwakarma
UKCRC Trials Unit:	Norwich Clinical Trials Unit
Latest Protocol:	Version 1, 21st December 2022

The purpose of the document is to specify the data analyses, prior to commencement, for the iACT4CARERS clinical trial. This document has been prepared by the Trial Statisticians, the Trial Manager and Chief Investigator (CI).

2. Abbreviations

ACT	Acceptance and Commitment Therapy
CACE	Complier Average Causal Effect
CBT	Cognitive Behavioral Therapy
CompACT	Comprehensive Assessment of Acceptance and Commitment Therapy Processes
CRF	Case Report Form
CSRI	Client Service Receipt Inventory
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
EACQ	Experiential Avoidance in Caregiving Questionnaire
FM	Fidelity Measure
GAD-7	General Anxiety Disorder-7
GCP	Good Clinical Practice
GP	General Practice
GSEM	Generalised Structural Equation Modelling
HEAP	Health Economics Analysis Plan
ICECAP-O	Icepop Capability Measure for Older People
ICH	International Council for Harmonisation
ITT	Intention-to-Treat
NCTU	Norwich Clinical Trials Unit
NHS	National Health Service
PHQ-9	Patient Health Questionnaire-9
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
REDCap	Research Electronic Data Capture
SAP	Statistical Analysis Plan
SD	Standard Deviation
STTS-R	Satisfaction With Therapy and Therapist Scale-Revised
TAU	Treatment-as-Usual
TSC	Trial Steering Committee
UEA	University of East Anglia

3. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion, with minimized bias or analytical deficiencies. Specifically, this plan has the following purpose to prospectively (a priori) outline the types of data analyses and presentations that will address the study objectives in the protocol, and to explain how the data will be handled and analysed, adhering to commonly accepted standards and practices of statistical analysis.

3.1 Background and rationale

Previous systematic reviews demonstrated that the prevalence of anxiety and depression in family carers of people with dementia is around 32% [1, 2]. These estimates are substantially higher than reported prevalence rates in the general population in the UK indicating a clear need for support with their mental health [3]. The current standard care pathway for mental health conditions in family carers of people with dementia includes self or GP referral to NHS psychological services [4]. However, many family carers are not able to access timely psychological support due to various barriers such as mobility issues, lack of respite care and a shortage of skilled therapists leading to long waiting lists [5]. One way to address the clear need for improved access, and also scalability, is to design a service that can be delivered remotely, accessed independently at home, and at times chosen by the carer. Online treatments can do this.

Acceptance and Commitment Therapy (ACT) is a form of psychotherapy with a strong evidence base for improving outcomes such as mood and quality of life in various populations, including people with anxiety, depression, chronic pain and somatic health problems [6-8]. ACT does not aim to change thoughts and feelings but rather to reduce avoidance and enhance personally meaningful behaviour. ACT achieves this by promoting psychological flexibility through three sets of skills, including the ability to (1) "step back" from restricting thoughts and allow painful emotions (i.e. OPEN); (2) focus on the present, connected with what is going on around us in the moment (i.e. AWARE); and (3) clarify and act on what is most important to do and build increasing patterns of effective values-based actions (i.e. ENGAGED) [9]. This strategic focus is highly practical because it is easier to change what we do, and how we do it, than to stop or change what we think. As such, it has been argued that ACT is particularly useful for those living with immutable and chronic conditions. Since many family carers also face uncontrollable circumstances, ACT may be well suited to this population.

Feasibility Testing

We received funding from the NIHR Research for Patient Benefit Programme (PB-PG-0418-20001) to (1) develop internet-delivered self-help ACT for family carers of people with dementia (iACT4CARERS), (2) explore whether iACT4CARERS is acceptable in this population and (3) test whether it is feasible to deliver iACT4CARERS within NHS services [10-12]. iACT4CARERS was offered on a self-learning basis, with minimal contact with a non-expert, minimally trained therapist.

Pre-defined criteria for progression from the feasibility study to a full-scale trial required iACT4CARERS to be deemed acceptable to family carers as indicated by uptake and initial engagement (recruitment of 30 eligible carers over 6 months, with ≥70% completing at least two online sessions). These criteria were

successfully met [10-12]. Participant recruitment took place from August 2020 and January 2021 during the COVID-19 pandemic with 108 carers referred across three sites over six months. Thirty-three eligible family carers were recruited, with ≥91% completing more than two sessions, suggesting excellent acceptability. There was preliminary evidence of improvements in anxiety, depression and psychological flexibility, particularly in anxiety, which demonstrated an average reduction of 26% on the GAD-7 anxiety scale (a reduction of 20% on GAD-7 is considered to be a Minimum Clinically Important Difference [13]).

The current study aims to undertake a definitive randomised controlled trial (RCT) with an internal pilot phase to determine the clinical and cost effectiveness of iACT4CARERS plus treatment as usual (TAU) compared to TAU alone in family carers of people with dementia who present with anxiety symptoms.

3.2 Objectives

This study aims to undertake a definitive RCT with an internal pilot phase to determine the clinical and cost effectiveness of iACT4CARERS plus TAU compared to TAU alone in family carers of people with dementia who present with anxiety symptoms.

4. Study Methods

4.1 Trial Design

This is a multi-site, single-blind, parallel, 2-arm RCT with ascertainment of clinical and cost effectiveness of iACT4CARERS plus TAU delivered over a 12-week period compared to TAU alone on family carers of people with dementia presenting anxiety symptoms. Primary and secondary outcomes will be evaluated at 12 weeks and 24 weeks post randomisation.

Trial data collection, randomisation, blinding and data analyses will be overseen by the Norwich CTU (NCTU).

4.2 Randomisation

Following baseline assessments, participants will be randomised on a 1:1 basis between iACT4CARERS plus TAU or TAU alone. Allocation will be computer-generated by a centralised system managed by NCTU ensuring concealment prior to randomisation. The sequence will be hidden from users of the database. Once allocated, a secure email will be sent to the Trial Manager and Research Lead at NCTU who will be unblinded. Minimisation will be performed with the factors collected at baseline: GAD-7 severity range (mild, moderate, severe) and ethnicity (Asian, Black, White, Mixed or Other ethnic groups). All unblinded study procedures will be conducted by the unblinded Trial Manager, NCTU Research Lead or the authorised delegate based at NCTU. Research Associates based elsewhere at UEA collecting baseline and follow-up data will be blinded to group allocation.

4.3 Sample size

Participants in our feasibility study had an average reduction of 26% on GAD-7. A reduction of 20% on GAD-7 is considered to be a Minimum Clinically Important Difference [13]. Using a conservative reduction of 20% from the mean baseline GAD-7 score, and using the variability estimated from our feasibility study, a clinically-meaningful effect size is estimated to be $d = 0.55$ for our sample. Recent systematic reviews of RCTs of self-help ACT and mindfulness-based interventions (mainly for individuals with a mental or physical health condition) demonstrated a pooled effect size of $d = 0.35$ for anxiety [14, 15]. One of these reviews, which solely focused on RCTs of self-help ACT [14] demonstrated that when analysis was limited to studies that utilised guided self-help ACT, the pooled effect size increased to $d = 0.61$, while limiting analysis to studies that used an unguided approach decreased the pooled effect size to $d = 0.16$. The effect size calculated from our feasibility study of iACT4CARERS, which utilised a guided approach, is in line with the effect size reported in previous reviews.

To ensure adequate statistical power, we have decided to take the most conservative approach possible and have used an effect size of $d = 0.35$ in our sample size calculation. To detect the effect size of d = 0.35 between the two trial arms at a two-tailed significant level of 5% with 90% statistical power, each arm requires 173 participants (i.e. 346 in total). Twenty seven percent of carers were lost to follow-up in our feasibility study. Assuming a dropout rate of 30%, a total of 496 carers will be recruited over 20 months (i.e. 24.8 participants per month).

4.4 Framework

iACT4CARERS is a multi-site, single-blind, parallel, 2-arm RCT using a frequentist approach to data analysis.

4.5 Interim analyses and stopping guidance

No efficacy interim analyses are planned. However, analysis of recruitment rates, withdrawal rates and treatment adherence rates will be conducted at intervals during the study for scrutiny by oversight committees. There are no formal stopping rules for the trial with regards to efficacy.

4.6 Timing of outcome assessments

The primary outcome is anxiety symptoms as assessed by the Generalized Anxiety Disorder-7 (GAD-7) at 12 weeks. The GAD-7, a validated self-report questionnaire [16], is the routine outcome monitoring tool for measuring anxiety symptoms used in the NHS. The GAD-7 will be completed at baseline, at 12 weeks post-randomisation and at 24 weeks post-randomisation.

5. Statistical Principles

All hypothesis testing will be at the two-sided 5% statistical significance level. Confidence intervals for parameter estimates will be at the corresponding 95% level. Analyses will be carried out by the trial statistician or delegated to an appropriately skilled statistician. Analysis will be blinded to group identity, (i.e. 'subgroup' blind). The Statistical Analysis Plan (this document) will be approved by the trial Data

Monitoring and Ethics Committee (DMEC) and the Trial Steering Committee (TSC) prior to any data analyses by the trial statistician. The lead health economist will develop a Health Economics Analysis Plan (HEAP) separately, which will also be reviewed by the DMEC and the TSC. Thus, the process for an economic evaluation is not described in this document. The process evaluation, including qualitative data analyses of interview transcripts, will be undertaken independently from the primary data analysis outlined in the SAP. Therefore, these procedures have not been described in this document.

5.1 Adherence and protocol deviations

All data will be collected irrespective of participant adherence. Should a participant withdraw consent or be lost to follow-up, all data will be included in the study dataset up to the point of consent withdrawal or loss to follow-up and will be included in the study database, unless explicitly refused by the participant. In case of any deviations observed, those deviations will be recorded within a REDCap system and undergo study team review.

The number and percentage of participants with significant protocol or ICH/GCP deviations will be summarised by treatment group for all the randomised participants. Participants will be counted once within each deviation category regardless of how many deviations they have in that category.

5.2 Analysis population

The primary analysis will be of the 'Intention-to-Treat' population (ITT) defined as all subjects randomised within the group to which they were allocated irrespective of treatment actually received or adherence to intended treatment [17].

If compliance is less than 80%, a sensitivity analysis, namely Complier Average Causal Effect (CACE) analysis will be carried out defining compliance as participant in the treatment arm completing at least six or more sessions. The population for CACE analysis will be those who comply with the intervention, specifically, those who comply in the intervention arm plus those in the TAU alone arm who would have complied had they been offered the intervention (see the "Sensitivity analysis" section for further details of CACE analysis).

6. Trial Population

6.1 Eligibility

There will be NO EXCEPTIONS (waivers) to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed PRIOR to attempting to randomise the participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only clinically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to

make future treatment decisions for other people with similar conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

6.1.1 Participant inclusion criteria

- Aged 18 years and over: The content of iACT4CARERS is written for adults as many family carers are in their 50s to 70s in the UK.
- Caring for a family member diagnosed with dementia: Any family members including in-laws, such as daughters-in-law, will be eligible. The diagnosis of dementia will be based on the clinical information provided by the participant (carer). Participants will be asked to confirm whether the care recipient has received a formal diagnosis of dementia from a relevant healthcare professional. Participants will also be asked to confirm whether they provide regular care (self-defined) to the care recipient. No criteria will be set for frequency of care they provide, such as hours of caring per week, as the psychological impact of caring is related to multiple factors such as the relationship they have with the person with dementia. For example, a son caring for his mother living with dementia who can only visit a few hours per week due to work could still be feeling that he is providing regular care and experiencing a high level of anxiety. We will collect background and demographic data such as frequency of care they provide and their relationship to the care recipient.
- Presenting anxiety symptoms: Participants will be asked to complete a measure of anxiety (General Anxiety Disorder-7: GAD-7 [16]) during the screening session. Those scoring in the clinical range of five or above will be eligible. Those scoring in the non-clinical range will be excluded to avoid a floor effect on the level of anxiety at baseline.
- Help-seeking: A brief description of the intervention will be included in the information sheet. Participants will be asked if they would like to receive help with their anxiety through iACT4CARERS. Only those who want to receive help will be eligible.
- Having access to internet: Participants will need to have access to a computer, tablet, or smartphone connected to the internet. iACT4CARERS is accessible from any platform on any device, except for those devices that use an old operating system no longer supported (e.g. Windows 7) as we cannot ensure the security of data. iACT4CARERS automatically blocks access from these unsupported devices.

6.1.2 Participant exclusion criteria

- Lacking capacity to provide fully informed written consent: The capacity to consent to participate in the study will be assessed and recorded using a Mental Capacity ACT (2005) assessment tool developed by Norfolk and Suffolk NHS Foundation Trust. Participants will not be included in the study if they are unable to provide this.

- Currently receiving ongoing formal psychological therapy: Participants will be asked to report any ongoing treatment they are receiving from healthcare services during the screening session. Participants currently receiving formal psychological therapy such as CBT, psychodynamic psychotherapy, systemic therapy and counselling will be excluded.
- Experiencing disabling medical or mental health problems making participation inappropriate or impractical: Participants will be asked to report any ongoing untreated condition during the screening session. Following the baseline assessment, the participant's GP will be informed of their involvement in the study, and any concerns raised by their GP regarding their involvement will be followed by a full discussion with the participant.
- Expressing active suicidal intent: The risk of suicide will be assessed during the screening session. This will be assessed using the suicide risk assessment protocol co-developed with Norfolk and Suffolk NHS Foundation Trust. This protocol has been used across multiple studies run by our team. Those presenting suicidal ideation with active intent will be excluded.

Potential participants with insufficient understanding of English to complete screening measures and engage in the intervention will be encouraged to bring a family member or a friend who can support the participant and act as an interpreter. This approach was recommended by PPI members from ethnic minority groups. If this option is not available, a professional interpreter can be arranged through the third company, which UEA already has a contract in place. If the study team needs to directly contact another family member or an interpreter regarding the participant such as arranging the appointment, verbal consent will be obtained from the participant for doing so.

6.2 Recruitment and participant flow

Patient recruitment and flow, starting from referral, screening, through follow up and inclusion in primary analysis, will be illustrated through a diagram as indicated in the Appendix, consistent with the CONSORT guidelines. Detailed summaries of reasons for non-attendance to screening and ineligibility will be presented in tables alongside the flow diagram. Additionally, the number of participants referred, screened and randomised by recruitment resources (i.e. NHS sites, Participant Identification Centres and other community resources such as local carer groups and Join Dementia Research) will also be reported.

6.3 Withdrawal

Withdrawal from the study between follow-up visits will be summarised with tables showing detailed reasons (if provided). Non-adherence to treatment does not constitute study withdrawal.

6.4 Baseline participant characteristics

A comparison will be made of baseline characteristics between the treatment groups. This will be through the use of summary statistics alone with no inferential analyses. The summaries of continuous variables will include the number of observations used, along with the mean, median, standard deviation, inter-quartile range, minimum, and maximum values, as deemed suitable for the

distributional form of the data. Categorical variable summaries will consist of the number of observations used, as well as the count and percentage of observations within each category.

We will focus our reporting and analysis on the overall scores obtained from each questionnaire. Sub-scales or domains will only be reported and analysed if specifically indicated otherwise.

The following participant variables will be reported at baseline (except for STTS-R which will only be collected at 12 weeks post-randomisation):

(i) Demographic details, including age, gender and ethnicity
(ii) Total GAD-7 score and GAD-7 severity range
(iii) PHQ-9
(iv) CompACT
(v) EACQ
(vi) STTS-R (treatment arm only)
(vii) EQ-5D-5L
(viii) ICECAP-O
(ix) Modification CSRI
(x) Expectations about treatment
(xi) Treatment preference

6.5 Treatment summary and compliance

The intervention involves participants completing a maximum of eight online sessions along with two one-to-one sessions via telephone or video call within a 12-week period. Participants who complete six or more online sessions will be considered treatment completers.

We will provide the following compliance summaries:

- Number and percentage of participants who attended various number of online sessions, categorised from 0 to 8 sessions.
- Mean (and SD), median, minimum, and maximum online sessions attended.
- Number and percentage of participants attending one or two one-to-one sessions, or none at all.
- A table detailing reasons for withdrawal from the intervention.
- Adherence rate, calculated by dividing the number of completers by the total number of participants allocated to the intervention group, regardless of the number of sessions completed.

7. Analysis

7.1 Outcome definitions

7.1.1 Primary outcome

The primary outcome is anxiety symptoms as assessed by the Generalized Anxiety Disorder-7 (GAD-7 [16]) at 12 weeks. In addition to the Mean (and SD), the proportions of participants falling into different severity ranges (mild, moderate, severe) at each time point will be reported.

7.1.2 Secondary outcomes

Clinical outcomes

- Patient Health Questionnaire-9 (PHQ-9 [18]): A 9-item self-report questionnaire assessing the severity of depressive symptoms. Both GAD-7 and PHQ-9 are used routinely in NHS psychological services for assessing recovery.
- Comprehensive Assessment of Acceptance and Commitment Therapy processes (CompACT [19]): A 23-item self-report questionnaire assessing psychological flexibility, which is commonly used in ACT studies. The total score and three subscale scores (Openness to Experience, Behavioural Awareness and Valued Action) will be used.
- Experiential Avoidance in Caregiving Questionnaire (EACQ [20]): A 15-item self-report questionnaire assessing experiential avoidance (one component of psychological flexibility) in the caregiving context. The total score and three subscale scores (Active Avoidant Behaviours, Intolerance of Negative Thoughts and Emotions Towards the Relative and valued action and Apprehension Concerning Negative Internal Experiences Related to Caregiving) will be used.
- Satisfaction With Therapy and Therapist Scale-Revised (STTS-R [21]): A 12-item self-report questionnaire assessing satisfaction with therapy and satisfaction with the therapist. The subscale scores (Satisfaction with therapy subscale, Satisfaction with the therapist and Outcome/Global improvement) will be used.

Cost-effectiveness measures (mainly to be used for a health economic analysis)

- EQ-5D-5L [22]): A 5-item self-report questionnaire assessing health-related quality of life.
- ICEpop Capability measure for Older people (ICECAP-O [23]): A 5-item questionnaire assessing capabilities that are required to have a high quality of life in older adults.
- Modified Client Service Receipt Inventory (modified CSRI [24]): An interview-based measure of health and social care service utilisation. This scale will be used to monitor TAU received in both arms during the trial and to calculate patient costs.

Potential Sources of bias

Expectations about treatment and participants' intervention arm preference are potential sources of bias that can affect treatment outcomes. These measures will be collected during the baseline session prior to randomisation, after participants are given a rationale for iACT4CARERS.

- Expectations about treatment: Two questions asking how much participants expect their symptoms and life to improve if they receive iACT4CARERS will be used (collected on a five-point Likert scale from 0 to 4).
- Treatment preference: Two questions asking how much they hope to receive iACT4CARERS and TAU alone without iACT4CARERS will be used (collected on a five-point Likert scale from 0 to 4).

Intervention fidelity measures

- ACT Fidelity Measure (ACT-FM [25]): All written feedback provided online by therapists will be recorded and randomly selected scripts will be reviewed and rated by independent ACT experts using an adapted form of the ACT-FM to check for intervention fidelity.
- Therapist response time: The time gap between the participant leaving a comment and their therapist providing a response will be collected for each session. Therapists are directed to provide feedback within three working days, where possible, but no later than five working days (i.e., before the next session is made available).

The scoring for each outcome measure is summarised in Table 1.

Table 1 Outcome measure scoring

Outcome variable	*Version number* *(if applicable)*	*Calculation required*	*Reference*
GAD-7		• Sum all 7 items to calculate the total score (ranges between 0 and 21). • Determine severity categories using the following cut-offs: Minimal (0-4), mild (5-9), 10-14 (moderate) and severe (15-21). • The total score and severity category for each participant are automatically recorded in REDCap. However, if one or more items are missing, these fields will be left blank.	[16]
PHQ-9		• Sum all 9 items to calculate the total score (ranges between 0 and 27). • The total score for each participant is recorded in REDCap. However, if one or more items are missing, this filed will be left blank.	[18]
CompACT		• Sum responses for each of the three subscales (Openness to Experience; Behavioural Awareness; Valued Action) and the scale as a whole (CompACT Total score). • Twelve items are reverse scored before summation (items 2, 3, 4, 6, 8, 9, 11, 12, 15, 16, 18, and 19). <u>*Openness to Experience (ranges between 0 and 60)*</u>	[19]

	• Calculated as the sum of scores for items: 2 (reversed), 4(reversed), 6(reversed), 8(reversed), 11(reversed), 13, 15(reversed), 18(reversed), 20, and 22. *Behavioural Awareness (ranges between 0 and 30)* • Calculated as the sum of scores for items: 3(reversed), 9(reversed), 12(reversed),16(reversed), and 19(reversed). *Valued Action (ranges between 0 and 48)* • Calculated as the sum of scores for items: 1, 5, 7, 10, 14, 17, 21, and 23. *CompACT Total (ranges between 0 and 138)* • Calculated as the sum of the three subscale scores. • The subscale and total scores are recorded in REDCap. However, if one or more items are missing, these fields will be left blank.	
EACQ	• Sum responses for each of the three subscales (Active Avoidant Behaviours; Intolerance of Negative Thoughts and Emotions Towards the Relative; Apprehension Concerning Negative Internal Experiences Related to Caregiving) and the scale as a whole (EACQ Total score). • Two items are reverse scored before summation (items 6 and 8). *Active Avoidant Behaviours (ranges between 6 and 30)* • Calculated as the sum of scores for items: 3, 7, 10, 11, 12, and 15. *Intolerance of Negative Thoughts and Emotions Towards the Relative (ranges between 4 and 20)* • Calculated as the sum of scores for items: • 1, 4, 2, and 5. *Apprehension Concerning Negative Internal Experiences Related to Caregiving (ranges between 5 and 25)* • Calculated as the sum of scores for items: 6(reversed), 9, 8(reversed), 13, and 14. *EACQ Total (ranges between 15 and 75)* • Calculated as the sum of the three subscale scores.	[20]

	• The subscale and total scores are recorded in REDCap. However, if one or more items are missing, these fields will be left blank.	
STTS-R	• Sum responses for each of the three subscales except for the Outcome subscale (Satisfaction with therapy; Satisfaction with the therapist; Outcome). *Satisfaction with therapy (ranges between 6 and 30)* • Sum the scores of all even number items. *Satisfaction with the therapist (ranges between (ranges between 6 and 30)* • Sum the scores of all odd number items excluding item 13. *Outcome/Global improvement (ranges 1 and 5)* • The score of item 13 alone. • The subscale scores are recorded in REDCap. However, if one or more items are missing, these fields will be left blank.	[21]
EQ-5D-5L	• The scores need to be calculated manually, outside REDCap for this scale. *EQ-5D-5L descriptive system* • This scale will be mainly used for the health economic analysis. For descriptive statistics, sum scores for each statement for total score (ranges between 5 to 25). Each statement is scored according to levels of perceived problems, coded as: I have no problems = 1; I have slight problems = 2, I have moderate problems = 3, I have severe problems = 4, I am unable to = 5. • Report frequency of each level reported (e.g., X% reported Level 1), or dichotomise the levels into 'no problems' (i.e. level 1) and 'problems' (i.e., levels 2 to 5) and reporting frequency of reported problems (source: https://www.unmc.edu/centric/_documents/EQ-5D-5L.pdf). *EQ-5D-5L visual analogue scale* • Report number entered by participant on scale of 0-100. Present both a measure of the central tendency and a measure of dispersion (mean and SD, or if skewed, median and 25th, 75th percentiles; source: https://www.unmc.edu/centric/_documents/EQ-5D-5L.pdf).	[22]

ICECAP-O	• The scores need to be calculated manually, outside REDCap for this scale. • This scale will be mainly used for the health economic analysis. For descriptive statistics, sum scores for each statement for total score (ranges between 5 to 25). Each statement is scored according to levels of perceived capability, coded as: I am able to do all of the things = 4; I am able to do many of the things = 3; I am able to do a few of the things = 2; I am unable to do any of the things = 1. • Report frequency of each level reported (e.g., X% reported Level 4).	[23]
Modification CSRI	• This scale will be mainly used for the health economic analysis. For descriptive statistics, report frequency of each response (e.g., X% providing up to 1 hours per week, X% 1-2 hours) or the central tendency and a measure of dispersion (e.g., support from other family carers in hours per week) depending on the nature of questions.	[24]
Expectations about treatment	• The score needs to be calculated manually, outside REDCap for this scale. • Sum responses for two five-point Likert scales (0 to 4). The total score ranges between 0 and 8.	NA
Treatment preference	• The score needs to be calculated manually, outside REDCap for this scale. • The second item is reverse scored before summation (#106 in REDCap). • Sum responses for two five-point Likert scales (0 to 4). The total score ranges between 0 and 8.	NA

7.2 Analysis methods

The primary analysis will be based on the Intention-to-Treat population. A linear mixed effects model for the GAD-7 at 12-week will be used for the primary effectiveness analysis. The model will include random intercepts for site and therapist with the therapist factor nested within sites. The analysis will define the site variable using the 20 NHS research sites that provided therapists. UEA, which functioned solely as a PIC site for self-referred participants, will not be included in this variable. Participants who initially signed up through UEA were reallocated to one of the 20 NHS sites (these allocations are recorded in REDCap under the site_allocation variable in the Site Allocation form). The model will be estimated via maximum likelihood method and the contributions of the random effects will be assessed via likelihood ratio test. Any of the random effects not having statistically significant contribution to the improvement of the model fit will be removed from the final analysis model. The estimated variance component(s) of the random effects remained (if any) in the final analysis model will be reported along with 95% confidence interval(s). If neither of the random effects contributes significantly to the model fit, the analysis model will be reduced to a standard multiple linear regression model. The model will include

the treatment group indicator as a fixed factor and will also account for the baseline outcome (GDA-7) and ethnicity (Asian, Black, White, Mixed or Other ethnic groups) as adjusting variables. If the residuals from the model do not follow a normal distribution, appropriate transformations of the outcome data will be considered, e.g., a logarithmic transformation in the case of a positively skewed distribution. The distribution of the residuals will be assessed visually and pertinent summary statistics (e.g., the skewness statistic) will be checked. Statistical significance will be set at 5% (two-sided). Parameter estimates will be presented with 95% confidence intervals.

The analyses of secondary outcomes such as PHQ-9, CompACT, and EACQ will follow an analogous approach. In each case, an appropriate linear mixed effects or linear regression model with inclusion of the random effects, outcome at baseline (if available), any potential confounding variables (e.g., participant characteristics showing significant imbalance at baseline between the trial arms), treatment group and minimisation factors (GAD-7 severity range of mild, moderate, severe and ethnicity groups of Asian, Black, White, Mixed or Other ethnic groups) will be constructed. The assumptions of the models, most notably the distribution of the residuals, will be assessed visually and with reference to pertinent statistics (e.g. the skewness statistic).

7.3 Sensitivity analyses

7.3.1 Sensitivity to missing data

Participants will be unable to submit any questionnaire with any missing fields when an online version of case report forms (CRFs) are used. Therefore, there will be no missing data from questionnaires completed online. This will be clearly explained in the information sheet. There may be some missing data when participants choose to use paper CRFs. Also, some missing data may result from loss to follow-up. A small percentage (5% or less) of missing data is generally inconsequential in which case we will carry out analysis of available data without imputation. For both the primary and secondary outcomes the extent and possible patterns of missing data will be checked. The relationship between baseline variables and missing primary outcome data will be examined. Additional data analysis will be undertaken in the event of missing data in the primary outcome and/or baseline covariates being more than 5%. A sensitivity analysis using multiple imputation will be considered to minimise potential bias affecting estimated treatment effect. Factors to include in the imputation model will be those that are likely to be related to the outcomes and those related to missingness. The imputation model will include the variables of the analytical model [26,27].

7.3.2 Sensitivity to inadequate compliance

As stated earlier, a CACE analysis will be performed to assess whether the estimated treatment effect from the primary analysis is influenced by inadequate (< 80%) compliance. The CACE analysis will be based on the comparison of the outcome measure between the observed compliers in the intervention (iACT4CARERS plus TAU) arm and the “would be” compliers in the control (TAU alone) arm. The “would be” compliers group is a counterfactual (or, unobserved) group, predicted probabilistically as those in the control group who would have complied had they been offered the intervention.

The CACE estimation will be implemented using the generalised structural equation modelling **(gsem)** procedure in Stata [28]. The gsem framwork for CACE estimation will encompass two models: (i) a linear model for the outcome with a Gaussian family and identity link function, and (ii) a latent class model with logit link for probabilistic prediction of compliance. The potential predictors of compliance in the latent class model will include information collected on extra-trial treatments, treatment expectation, treatment preference along with baseline GAD-7 severity and ethnicity.

7.3.3 Sensitivity to referral routes

This sensitivity analysis will be carried out if the distribution of participants from the two referral routes (self-referred and health care staff referred) differs between the two intervention arms at baseline. The analysis will define the referral route variable based on the referral site information. Participants whose source of referral is recorded as UEA are all self-referred, while those recorded as one of the 20 NHS sites are health care staff referred. This information is recorded in the referral_site variable in the Referral form in REDCap. Any potential confounding bias in the estimated treatment effect due to referral route will be assesses by including a binary indicator of the referral route (0=self-referred, and 1= health care staff referred) in the primary ITT analysis model as an additional covariate.

7.3.4 Sensitivity to treatment expectation/treatment preference

Similar to the sensitivity analysis of referral routes, baseline balance of treatment expectation and treatment preference measures will be assessed via descriptive statistics. If a difference is observed at baseline, any potential confounding bias by these variables will be accounted for in the ITT analysis model by including them as additional covariates.

7.4 Additional exploratory analyses

The following exploratory analyses will be carried out considering factors that may influence the finding (therapist fidelity, the number of sessions completed, change in psychological flexibility).

- **Therapist fidelity:** The ACT-FM produces ACT consistency and inconsistency scores for each therapist. Therapist response time will be collected for each participant for every session. Descriptive statistics will be used for the ACT-FM scores and therapist response time to summarise therapist fidelity.
- **Treatment completion:** The number of sessions completed (ranges 0-8) by each participant will be used to explore if these have any influence on treatment outcomes. Descriptive statistics will be used to summarise the number of sessions completed.
- **Psychological flexibility:** The CompACT scores (total score and subscale scores) will be analysed to determine if changes from 0 to 12 week and 0 to 24 weeks influence outcomes at each time point. It is hypothesised that greater psychological flexibility is associated with better clinical outcomes.

A correlation analysis will be conducted for intervention arm to explore any association of primary outcome (i.e., GAD-7) with therapist fidelity, number of sessions completed and change in psychological flexibility separately.

7.4 Subgroup analyses

No subgroup analyses are planned.

7.5 Deviations from planned analysis

Should any additional statistical analyses be required during the final analysis, appropriate methods will be used, and any changes, including the rationale for use, will be documented in the clinical study report or manuscript.

7.6 Safety data

Safety data (adverse events reported from time of first exposure to treatment to end of treatment) will be summarised by group. Any serious adverse events will be described in full including possible relationship to the treatment.

Serious adverse events related or unrelated to the intervention, will be analysed using a logistic regression model with the random effects, pre-specified prognostic variables and treatment group as explanatory variables.

8. Description of Tables and Figures

All data up to the time of study completion/withdrawal from the study will be included in the analysis, regardless of duration of treatment.

All raw data will be presented to the original number of decimal places. The mean and standard deviation will be presented with to 2 decimal places or 3 significant figures depending upon the nature of the data. Percentages will be presented in to 1 decimal place. All categories of variables will be presented even if there is no data. Blank cells, were data are not expected, will be filled by "-" in reporting of results.

Precision of p-values will be 3 decimal places, i.e. p-values less than 0.001 will be presented as <0.001 and if equal to 1 then ≥ 0.999.

9. Software

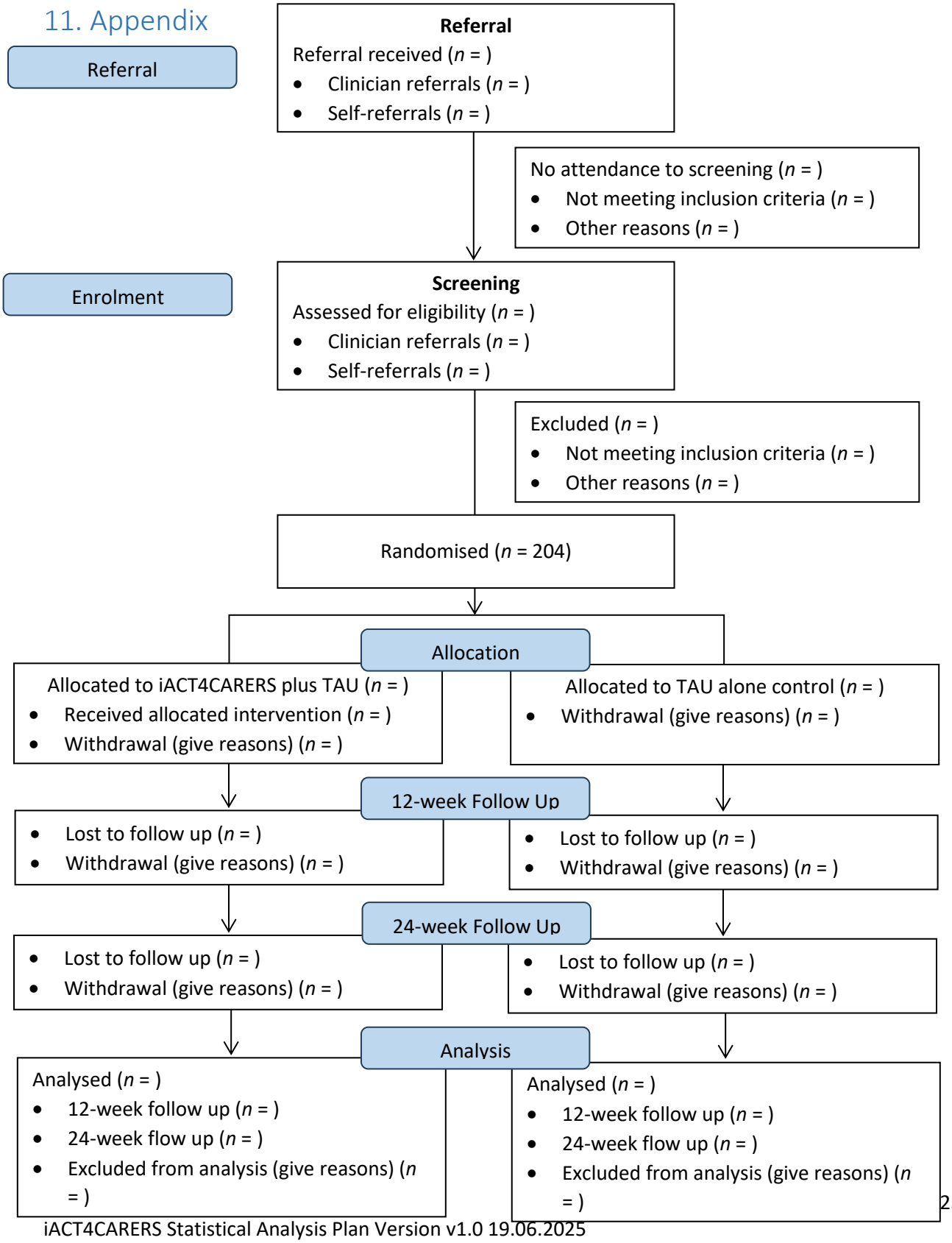
All analysis will be performed using SAS® Software version 9.4 and Stata version 17.

10. References

1. Collins, R. and N. Kishita, *Prevalence of depression and burden among informal caregivers of people with dementia: A meta-analysis.* Ageing and Society, 2020. **40**(11): p. 2355-2392.
2. Kaddour, L. and N. Kishita, *Anxiety in informal dementia caregivers: a meta-analysis of prevalence.* Journal of Geriatric Psychiatry and Neurology, 2020. **33**(3): p. 161-172.
3. McManus, S., et al., eds. *Mental health and wellbeing in England: Adult psychiatric morbidity survey 2014*. 2016, NHS Digital: Leeds, UK.
4. National Institute for Health and Care Excellence, *NICE guideline [NG97] Dementia: assessment, management and support for people living with dementia and their carers*. 2018, NICE: London, UK.
5. Alzheimer's Society, *Dementia 2014: Opportunity for change*. 2014, Alzheimer's Society: London, UK.
6. A-Tjak, J.G.L., et al., *A meta-analysis of the efficacy of acceptance and commitment therapy for clinically relevant mental and physical health problems.* Psychotherapy and Psychosomatics, 2015. **84**(1): p. 30-36.
7. Hann, K.E.J. and L.M. McCracken, *A systematic review of randomized controlled trials of Acceptance and Commitment Therapy for adults with chronic pain: Outcome domains, design quality, and efficacy.* Journal of Contextual Behavioral Science, 2014. **3**(4): p. 217-227.
8. Gloster, A.T., et al., *The empirical status of acceptance and commitment therapy: A review of meta-analyses.* Journal of Contextual Behavioral Science, 2020. **18**: p. 181-192.
9. Hayes, S.C., et al., *Acceptance and commitment therapy and contextual behavioral science: Examining the progress of a distinctive model of behavioral and cognitive therapy.* Behavior Therapy, 2013. **44**(2): p. 180-198.
10. Kishita, N., et al., *Internet-delivered guided self-help Acceptance and Commitment Therapy for family carers of people with dementia (iACT4CARERS): A feasibility study.* Aging and Mental Health, 2022. **26**(10): p. 1933-1941.
11. Contreras, M.L., et al., *Internet-delivered guided self-help Acceptance and Commitment Therapy for family carers of people with dementia (iACT4CARERS): A qualitative study of carer views and acceptability.* International Journal of Qualitative Studies on Health and Well-being, 2022. **17**(1): p. 2066255.
12. Contreras, M.L., et al., *Therapists' perceptions and acceptability of providing internet-delivered guided self-help Acceptance and Commitment Therapy (ACT) for family carers of people with dementia (iACT4CARERS): a qualitative study.* The Cognitive Behaviour Therapist, 2021. **14**: p. e38.
13. Kounali, D., et al., *How much change is enough? Evidence from a longitudinal study on depression in UK primary care.* Psychological Medicine, 2020. **52**(10): p. 1-8.
14. French, K., N. Golijani-Moghaddam, and T. Schröder, *What is the evidence for the efficacy of self-help acceptance and commitment therapy? A systematic review and meta-analysis.* Journal of Contextual Behavioral Science, 2017. **6**(4): p. 360-374.
15. Cavanagh, K., et al., *Can mindfulness and acceptance be learnt by self-help?: A systematic review and meta-analysis of mindfulness and acceptance-based self-help interventions.* Clinical Psychology Review, 2014. **34**(2): p. 118-129.

16. Spitzer, R.L., et al., *A brief measure for assessing generalized anxiety disorder: the GAD-7.* Archives of Internal Medicine, 2006. **166**(10): p. 1092-1097.
17. International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, *Guideline for Industry, Structure and Content of Clinical Study Reports (ICH E3)*. 1996, ICH: Geneva, Switzerland.
18. Kroenke, K., R.L. Spitzer, and J.B. Williams, *The PHQ-9: validity of a brief depression severity measure.* Journal of General Internal Medicine, 2001. **16**(9): p. 606-613.
19. Francis, A.W., D.L. Dawson, and N. Golijani-Moghaddam, *The development and validation of the Comprehensive assessment of Acceptance and Commitment Therapy processes (CompACT).* Journal of Contextual Behavioral Science, 2016. **5**(3): p. 134-145.
20. Losada, A., et al., *Development and validation of the Experiential Avoidance in Caregiving Questionnaire (EACQ).* Aging & Mental Health, 2014. **18**(7): p. 897-904.
21. Oei, T.P.S. and A.L. Green, *The Satisfaction With Therapy and Therapist Scale-Revised (STTS-R) for group psychotherapy: Psychometric properties and confirmatory factor analysis.* Professional Psychology: Research and Practice, 2008. **39**(4): p. 435-442.
22. Herdman, M., et al., *Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L).* Quality of Life Research, 2011. **20**(10): p. 1727-1736.
23. Grewal, I., et al., *Developing attributes for a generic quality of life measure for older people: Preferences or capabilities?* Social Science & Medicine, 2006. **62**(8): p. 1891-1901.
24. Beecham, J. and M. Knapp, *Costing psychiatric interventions*, in *Measuring Mental Health Needs* G. Thornicroft, Editor. 2001, Gaskell: London. p. 200-224.
25. O'Neill, L., et al., *The development of the Acceptance and Commitment Therapy Fidelity Measure (ACT-FM): A delphi study and field test.* Journal of Contextual Behavioral Science, 2019. **14**: p. 111-118.26. Yan, X., S. Lee, and N. Li, *Missing data handling methods in medical device clinical trials.* Journal of Biopharmaceutical Statistics, 2009. **19**(6): p. 1085-1098.
27. Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, *E9(R1) Statistical principles for clinical trials: Addendum: Estimands and sensitivity analysis in clinical trials*. 2021, CDER and CBER: MD, USA.28. Troncoso, P. and A. Morales-Gómez, *Estimating the complier average causal effect via a latent class approach using gsem.* The Stata Journal, 2022. **22**(2): p. 404-415.

11. Appendix


Referral
Referral
Referral received (n =)
Clinician referrals (n =)
Self-referrals (n =)
No attendance to screening (n =)
Not meeting inclusion criteria (n =)
Other reasons (n =)
Enrolment
Screening
Assessed for eligibility (n =)
Clinician referrals (n =)
Self-referrals (n =)
Excluded (n =)
Not meeting inclusion criteria (n =)
Other reasons (n =)
Randomised (n = 204)
Allocation
Allocated to iACT4CARERS plus TAU (n =)
Received allocated intervention (n =)
Withdrawal (give reasons) (n =)
Allocated to TAU alone control (n =)
Withdrawal (give reasons) (n =)
12-week Follow Up
Lost to follow up (n =)
Withdrawal (give reasons) (n =)
Lost to follow up (n =)
Withdrawal (give reasons) (n =)
24-week Follow Up
Lost to follow up (n =)
Withdrawal (give reasons) (n =)
Lost to follow up (n =)
Withdrawal (give reasons) (n =)
Analysis
Analysed (n =)
12-week follow up (n =)
24-week flow up (n =)
Excluded from analysis (give reasons) (n =)
Analysed (n =)
12-week follow up (n =)
24-week flow up (n =)
Excluded from analysis (give reasons) (n =)