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

Health Economics Analysis Plan (HEAP)

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Name	Role	Signature	Date
David Turner	Health Economics Lead	Signed	19 June 2025
Naoko Kishita	Chief Investigator	Signed	19 June 2025

The HEAP was drafted by David Turner and agreed by Naoko Kishita. The following individuals also commented on the draft version of this HEAP: Adam Wagner (health economist); Garry Barton (health economist); Mizanur Khondoker (study statistician)

Section 1. Administrative information

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Chief Investigators: Dr Naoko Kishita

Trial Health Economist: David Turner

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Latest Protocol : Version 1, 21/12/2022

Latest SAP: Statistical Analysis Plan, Version 1.0.

Trial HEAP version: V1.1

Purpose of the Health Economics Analysis Plan (HEAP)

The purpose of this HEAP is to describe in detail the methods used to analyse the health economic data collected as part of the iACT4CARERS trial. The HEAP is designed to ensure that there is no conflict with the protocol (Version 1.0) and associated Statistical Analysis Plan (SAP, version v1.0) and it should be read in conjunction with them.

Section 2. Trial introduction and background

2.1 Background and Rationale

This is provided in section 5.1 of the protocol. A brief summary follows. The prevalence of anxiety and depression in carers of people with dementia is substantially higher than the reported prevalence in the general population in the UK. However, many carers may find it difficult to access timely psychological support due to a variety of barriers: examples include lack of skilled therapists, shortage of respite care, and mobility issues. A potential solution to this would be a service that could be delivered remotely, accessed independently at home, at times convenient to the carer. These characteristics can be provided by online services. This requires a psychological intervention that can be: a) delivered online in a self-help format and; b) effectively targets anxiety, the primary outcome of this study. Acceptance and Commitment Therapy (ACT) is a form of psychotherapy with a strong evidence base for improving outcomes such as mood or quality of life. Additionally, ACT has been proven effective when delivered online in a self-help format for the general population. A feasibility study was conducted to: a) develop an internet-delivered self-help ACT tailored for family carers of people with dementia (iACT4CARERS); b) explore acceptability of iACT4CARERS; c) test feasibility of delivery of

iACT4CARERS within NHS services. This was conducted successfully and led to the current study which is a definitive randomised controlled trial (RCT) with an internal pilot to determine the clinical and cost-effectiveness of iACT4CARERS plus treatment as usual (TAU) compared to TAU alone.

2.2 Objectives

The overall trial aim from section 5.2 of the protocol:

“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.”

The HEAP will cover the health economic aspects of these objectives only, i.e., the process of estimating cost-effectiveness.

2.3 Trial design

The study is a multi-centre, single blind, parallel, 2-arm randomised controlled trial comparing iACT4CARERS plus TAU compared to TAU alone. Participants will be randomised on a 1 to 1 basis. Participants can be included if they are: ≥ 18 years of age; caring for a family member diagnosed with dementia; present with anxiety symptoms (assessed with GAD7, scoring 5 or above); help-seeking to manage anxiety; and have access to the internet. They will be excluded if they: lack capacity to provide fully informed written consent; are currently receiving formal psychological therapy; experiencing disabling medical or mental health problems; and expressing active suicidal intent. The primary outcome measure will be anxiety symptoms evaluated using the GAD7 at the studies 3 data collection timepoints: baseline; 12; and 24 weeks post randomisation. Participants can be recruited to the study via different routes. Recruitment methods include: participant Identification Centres (PICS); NHS sites; community based recruitment; and culturally acceptable recruitment strategies (as recommended by PPI members). Methods would include targeted recruitment by interrogating databases. Participants will also be recruited by

advertising and working with partner organisations to make the study known to a large number of individuals. The target sample size is 248 per group or 496 in total.

2.3.1 Comparators

Internet-delivered self-help Acceptance and commitment therapy (iACT4CARERS) consists of eight online sessions. Sessions have three phases: self-learning; reflection; and practice, designed to facilitate participants' acquisition and application of ACT skills in daily life. Trial therapists will be mainly Band 4 NHS staff and will provide individually tailored written feedback. In addition to online sessions participants are offered two 30-minute one-to-one optional sessions delivered by telephone or video call. iACT4CARERS will be offered in addition to TAU. The control group receives TAU only. This normally consists of information, brief education, practical advice, contacts for local carer support groups, and/or respite care.

Section 3. Economic approach/overview.

3.1 Aim and objectives of the economic evaluation.

The aim of the economic evaluation is to determine whether iACT4CARERS plus TAU represents an efficient use of health care resources when compared to TAU alone – i.e., is this something the United Kingdom National Health Service (NHS) should routinely be investing resources into providing?

3.2 Objective(s) of economic evaluation.

- To estimate the intervention and health care costs associated with each of the study groups, and to estimate incremental cost differences between the two groups.
- To estimate quality adjusted life years (QALYs) generated over the 24-week follow-up for iACT4CARERS + TAU and for TAU alone, to enable an estimate of the incremental differences between interventions.
- To carry out a cost-utility analysis of iACT4CARERS + TAU compared to TAU alone.

- To estimate outcomes in terms of changes in the primary outcome of GAD-7 of the study. This will comprise a cost-effectiveness study estimating the additional cost per point improvement in the GAD-7.

3.3 Overview of the economic analysis.

The proposed economic analysis will be a 'within trial' analysis. The term 'within-trial' means that analysis will be conducted using data obtained from iACT4CARERS participants within the time frame of follow-up in this trial (24 weeks). The economic analysis will be performed using individual patient level data from iACT4CARERS. Two types of economic evaluations will be performed. Firstly, we will conduct a cost-utility study using the outcome of QALYs. This will comprise the primary or base-case analysis. Secondly, we will conduct a cost-effectiveness analysis using the GAD-7 primary outcome measure These will be presented as a secondary analysis as part of the sensitivity analysis, see section 5.12. Evidence from iACT4CARERS will enable incremental cost-utility and cost-effectiveness ratios to be calculated by taking a ratio of the difference in the mean costs and mean QALY (cost-utility study) or mean effects (cost-effectiveness study).

3.4 Jurisdiction

iACT4CARERS has been conducted within the UK and operates within the UK NHS.

3.5 Perspective(s)

The primary economic analysis will be that of the NHS and personal social services, as recommended by the National Institute for Health and Care excellence (NICE) (1) . This will include costs borne by primary and secondary care. Additionally, further information has been requested from participants to include wider costs, including out-of-pocket expenses by individuals.

3.6 Time horizon(s)

The health economic analysis has a time horizon of 24-weeks, the follow-up period in iACT4CARERS.

Section 4. Economic data collection and management

4.1 Statistical Software

The analysis will be conducted in Microsoft Excel; IBM SPSS statistics, version 28 or higher; and Stata version 17 or higher.

4.2 Identification of resources.

We will record resources required to provide the iACT4CARRERS intervention. The resource use to be measured falls under a number of categories. Providing the on-line sessions will require resources to provide the website through which the intervention would be provided. This will include set-up and any resources required for maintaining or updating the site. We will also record resources required to provide therapist support. These will include the cost of providing required training, time required to provide supervision by the clinical psychologist, the number of direct contact sessions provided to participants and time spent responding to any participant questions. In terms of costing the intervention we will not include costs incurred in developing the interventions. These costs can be considered 'sunk', i.e., they will already be incurred and cannot be recovered. In terms of the decision to implement the intervention then relevant costs would only be those that would be needed to be incurred or those that are consequences of implementation (e.g., changes in service use).

Secondly, we will record resources associated with health and social care received by the participant (carer). These will be obtained using a modified client service receipt inventory (CSRI), administered at baseline, 12, and 24 weeks (2). The period of recall is 'the past 3-months'. The modified CSRI will focus on resource use by the carer. Items covered are the following. Secondary care services such as stays in hospital, visits to A&E and use of hospital outpatient services. Use of health and social care services (GP; GP at home; Practice nurse; mental health nurse, psychiatrist, psychologist, social worker or care manager; occupational therapist; district nurse; counsellor; mental health team worker; other to be specified by respondent). The questionnaire will also cover use of some dementia related services or support, by the person with dementia. This would include the following: respite care short term stays; day care centre; sitting service; support worker for the

person with dementia at home, with or without personal care; carer support groups; dementia cafe; lunch club; and other services to be specified by the respondent. The CSRI will also ask about time the carer spends looking after the person with dementia as well as potential effects on productivity costs (time-off work). We will also ask the carer about use of medicines related to mental health, and use of mental health therapies.

4.3 Valuation of resource-use data

All items of resource use identified will be combined with an appropriate unit cost to estimate costs for each item in each group. For health care contacts, unit costs will be taken from three main sources. Firstly, we will use the NHS reference costs for costs of inpatient stays and outpatient stays as well as A&E contacts (3). As we do not ask specifics regarding the reason for secondary care a weighted average cost will be estimated. Weighted average costs are provided by NHS reference costs and are the sum of costs for all items in the reference costs for a particular category divided by the total number of those events. For other items of health care resource use we will take values of unit costs from estimates of unit costs published by the Universities of Kent and York(4). For drug costs a cost will be taken from the prescription Cost Analysis (PCA) (5). For time-off work we will use national averages earnings. Where possible, costs for study specific costs such as training of therapists will be obtained from study records on expenditure and delivery of training. As will any directly incurred costs of hosting the web-site. The most recent available cost year will be used at the time of analysis. Where available costs fall outside this cost year, they will either be inflated or deflated using an appropriate measure of inflation.

4.4 Identification of outcome(s)

The primary outcome measure used in the cost-utility study will be the QALY. This will be the primary or base case analysis. We will also estimate utilities using the ICECAP-O, for use in a sensitivity analysis (see section 5.12). Secondly, we will also conduct a cost-effectiveness study using the GAD-7.

4.5 Measurement of outcome(s)

QALYs will be estimated using the EQ-5D-5L (6). This will be obtained at baseline, 12, and 24 weeks from randomisation. This will represent the main (base case) analysis. The ICECAP-O will also be used as a measure of utility measure (7). For the cost-effectiveness study the GAD-7 will be used to estimate scores in the two intervention groups at 24-weeks.

4.6 Valuation of outcome(s)

To obtain QALYs from the EQ-5D-5L, a UK based valuation system is required to convert the item scores into a utility-based score. This has the anchor points of 1 (full health) and zero (dead), but negative scores are also possible. Currently there are three main options for obtaining UK utility values for the EQ-5D-5L. These are the algorithm published by Devlin and colleagues (8); values mapped using a 'cross-walk' method from the EQ-5D-3L value set (9); and a mapping function developed by Hernández Alava and colleague (10). Current guidance from the National Institute for Health and Care excellence (NICE) recommends valuation using the method proposed in Hernandez et al, and this will be used in this analysis (1). The ICECAP-O will be valued using a published algorithm (7).

Section 5. Economic data analysis

5.1 Analysis population

The analysis will be on an intention to treat (ITT) basis.

5.2 Timing of analysis

The analysis will occur once all health economic data has been collected and entered into the study databases. There will be no interim analysis.

5.3 Discount rates for costs and benefits

Discounting allows for the differential timing of both costs and benefits. It means that costs and benefits that occur in the future are valued less than those that occur today. The convention in economic evaluations is not to use discounting where the

time frame of analysis is one year or less. As the duration of follow-up in the current study is 24 weeks, discounting will not be used.

5.4 Cost-utility threshold(s)

The analysis will generate an estimate of the incremental cost per additional QALY derived. To consider whether this then represents a cost-effective intervention and hence represents a good use of health care resources a value of a QALY for decision making is needed. It is intended to use the NICE threshold range of £20,000 to £30,000 pounds per QALY in evaluating cost-effectiveness (11).

5.5 Analysis of resource use and cost

Differences in the use of health care resources between randomised interventions will be described but not formally tested. Estimates of resource use will be combined with estimates of unit cost. A total cost for each type of health care resource use will be estimated. Costs across the range of different resource types will be summed to form an estimate of total cost in each intervention. Estimates of mean costs for each resource item as well as mean total cost will be presented with 95% confidence intervals.

5.6 Analysis of outcomes

Mean EQ-5D-5L scores for each timepoint in each trial intervention will be calculated alongside 95% confidence intervals. QALYs will be calculated by means of area under the curve at each of the 3 time points of baseline, 12, and 24 weeks. The same process will be carried out with the ICECAP-O. The base case analysis will use QALYs generated by means of the EQ-5D-5L, with ICECAP-O values used in a sensitivity analysis. We will also conduct a cost-effectiveness study using the GAD-7 score at 24 weeks and will estimate the additional cost per point improvement in the GAD-7.

5.7 Data cleaning for analysis

As part of the process of calculating costs and outcomes face validity checks will be carried out on the data. Where possible, anomalous values will be checked against source documents.

5.8 Missing data

Missing data can be a particular issue in health economic data as both cost and outcomes tend to be aggregates of other variables. For example, a QALY can only be calculated if an individual has values for EQ-5D-5L scores at all 3 time points. If EQ-5D-5L scores are not missing at random then this can introduce bias.
We will analyse the patterns of missing data and the number of participants with missing data. The appropriate method for dealing with missing data will depend on the proportion of missing data and likely mechanism of missingness (14). However, a priori, we would expect to use multiple imputation methods to estimate missing data. A priori, we would also expect the imputed analysis to comprise the base-case because of the risk of bias associated with a complete case analysis. Guidelines on handling missing data in economic evaluations will be followed (12). .

5.9 Analysis of cost-effectiveness

The estimate of cost-utility and cost-effectiveness will be evaluated using regression based methods to allow for the effect of baseline characteristics. We will use seemingly unrelated regression (sureg) in Stata to estimate costs and benefits allowing for any correlation between them. For QALYs, results will be adjusted for baseline EQ-5D-5L score. A similar approach will be taken for costs but these will be adjusted for baseline costs. We will also follow, as far as possible, the methods used in the statistical analysis in terms of what baseline characteristics the analysis is adjusted for. For both costs and outcomes, study group will be included in the regression equations. These estimates of incremental cost and effect derived for the study intervention compared to the comparator group will then be used to estimate cost-effectiveness. Cost and QALY data will be combined to calculate an incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) statistic from the

NHS perspective, this will be the base case analysis. Values obtained will be compared to the NICE threshold outlined in section 5.4. Additional information for the patient questionnaire will be used to broaden the perspective this will be presented as a sensitivity analysis. Where appropriate, an ICER for the iACT4CARERS group will be estimated compared to the control. However, if it is found that one group dominates another (i.e., is both more effective and less costly) then ICERs will not be estimated, as is standard practice. Differences in results produced will be compared with the primary outcome measure and this will be considered in the interpretation of results.

5.10 Sampling uncertainty

The nonparametric bootstrapping approach will be used to determine the level of sampling uncertainty surrounding the mean ICER by generating multiple estimates of incremental costs and benefits. Where multiple imputation is used this will be carried out for each imputed data set. This uncertainty will be represented in graphical form by generating scatter plots of costs and benefits for iACTCARERS+TAU compared to TAU. Additionally, we will calculate cost-effectiveness acceptability curves (CEAC) to show the probability that iACT4CARERS is cost-effective compared to the control group at values of a QALY ranging from £0 to £50,000. Similarly, a CEAC will be estimated for the cost-effectiveness analysis showing cost per point improvement in the GAD-7.

5.11 Subgroup analysis or analyses of heterogeneity

In line with the SAP, no subgroup analyses are planned.

5.12 Sensitivity/Scenario analysis

Several different scenarios will be presented.

- An analysis will be presented based on a utility estimate derived from the ICECAP-O.
- A complete case analysis (CCA) will be presented showing only cases for which we do not have missing data.

- Data on productivity costs will be included to take a broader perspective.
- A sensitivity analysis will be included to cover variations in the cost of the intervention related to differences in assumptions on throughput and how the intervention is delivered.

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