



Li, J., Wu, Q., Parrott, S., Tallon, D., & Wiles, N. J. (2024). *Multi-centre randomised controlled trial of integrated therapist and online CBT for depression in primary care (INTERACT RCT): Health Economics Analysis Plan.*

Publisher's PDF, also known as Version of record

[Link to publication record in Explore Bristol Research](#)
PDF-document

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>



Li, J., Wu, Q., Parrott, S., Tallon, D., & Wiles, N. J. (2024, Jan 4). Multi-centre randomised controlled trial of integrated therapist and online CBT for depression in primary care (INTERACT RCT): Health Economics Analysis Plan. Unpublished. University of Bristol.

Publisher's PDF, also known as Version of record

[Link to publication record in Explore Bristol Research](#)
PDF-document

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>



INTERACT RCT

**Multi-centre randomised controlled trial of integrated therapist
and online CBT for depression in primary care**

HEALTH ECONOMICS ANALYSIS PLAN

Version v1.0

York Trials Unit

Department of Health Sciences

University of York

York, YO10 5DD

Version date: 4th Jan. 24

Author(s): Jinshuo Li, Qi Wu, Steve Parrott

Chief Investigator: Professor Nicola Wiles

Research Programme Manager: Debbie Tallon

Contents

1	REVISIONS	3
2	GENERAL.....	3
2.1	Document scope	3
2.2	Glossary.....	3
3	TRIAL SUMMARY	4
3.1	Aim and objectives.....	4
3.2	Design.....	4
4	Outcomes and data collection.....	5
4.1	Costs	5
4.1.1	Intervention and comparator costs	5
4.1.2	Healthcare and social services costs for mental health	7
4.1.3	Participants’ out-of-pocket spending	8
4.1.4	Participants and/or informal carers’ lost income	8
4.1.5	Benefits	8
4.2	Effectiveness measures	9
4.2.1	Quality-Adjusted Life Years.....	9
5	ANALYSIS	9
5.1	Methods overview	9
5.2	Missing data	10
5.3	Primary analysis	10
5.4	Secondary analysis	11
5.4.1	Cost-effectiveness analysis from participants’ and informal carers’ perspective 11	
5.4.2	Cost-effectiveness analysis from societal perspective	12
5.5	Sensitivity analyses	12
6	SIGNATURES OF APPROVAL	14

7 REFERENCES 15

1 REVISIONS

Version	Date	Summary of changes
1.0	04.01.2024	Initial draft

2 GENERAL

2.1 Document scope

The current document describes the planned analyses of economic evaluation alongside the INTERACT RCT.

This analysis plan has been checked for consistency with the INTERACT trial protocol v2.0 (24 March 2023) (1).

2.2 Glossary

BDI-II Beck Depression Inventory

CBT Cognitive Behavioural Therapy

cCBT Computerised Cognitive Behavioural Therapy

CEA Cost-effectiveness analysis

CEAC Cost-effectiveness acceptability curves

IAPT Improved Access to Psychotherapies

MAR Missing At Random

MI Multiple imputation

MNAR Missing Not At Random

NHS National Health Service

NICE National Institute for Health and Care Excellence

PSS Personal Social Service

QALY Quality-adjusted Life Year

3 TRIAL SUMMARY

The following sections briefly describe the INTERACT RCT. Full details please see the published protocol (v2.0, 24/03/2023) (1).

3.1 Aim and objectives

The aim of the economic evaluation is to establish the cost-effectiveness of an integrated approach to delivering CBT in reducing depressive symptoms and improving quality of life over and above usual care over 12 months for primary care patients with depression.

Specific objectives are:

- To describe the components and estimate the costs of the integrated therapist and online CBT in the trial;
- To assess the costs of healthcare service use for mental health following the intervention;
- To conduct an incremental cost-effectiveness analysis of the integrated therapist and online CBT over and above usual care from an NHS and personal and social services (PSS) perspective;
- To explore the cost-effectiveness of the integrated therapist and online CBT over and above usual care from patients and informal carers perspective;
- To explore the cost-effectiveness of the integrated therapist and online CBT over and above usual care from a societal perspective.

3.2 Design

The INTERACT RCT is a pragmatic, two parallel group, multi-centre superiority randomised controlled trial with allocation at the level of individual.

The trial was set in primary care in three centres: University of Bristol, University College London, and Universities of Hull/York. Participants were recruited from GP practices in the surrounding areas of the three centres.

The inclusion criteria were: 1) aged 18 years old or above; 2) scored 14 or higher on Beck Depression Inventory (BDI-II); and 3) meet ICD-10 criteria for a diagnosis of depression using CIS-R.

Participants were excluded if they suffered from alcohol or substance dependency in the past year; were diagnosed with bipolar disorder, schizophrenia, psychosis, or dementia; were currently under psychiatric care (including those referred but yet to be seen) for depression; cannot complete questionnaires unaided or would require an interpreter; were currently receiving CBT or other psychotherapy; have received high-intensity CBT in the past four years; were taking part in another intervention trial; or were unwilling or unable to receive CBT via computer/laptop/smartphone.

The sample size was set at 434. Participants were randomised to one of the two groups using at 1:1 ratio, stratified by centre and minimised on gender, current antidepressant use, and depression severity using BDI-II tertiles.

After baseline, follow-up assessments are conducted at 3-, 6-, 9-, and 12-months post-randomisation, with longer questionnaires at 6- and 12 months post-randomisation. Different measures are administered at each follow-up. The measures related to the economic evaluation are presented in the following section. A detailed schedule of all measures used is given in the published protocol (1).

4 OUTCOMES AND DATA COLLECTION

4.1 Costs

The costs from the NHS and PSS perspective comprise costs of the intervention (integrated therapist and online CBT) and comparator (usual care), primary, community and secondary health care for mental health, and social services for mental health.

The costs from patients and informal carers comprise payments for private treatments and remedies for mental health, transport spending of return journey to GP, and lost income of participants and/or their informal carers.

The costs from the societal perspective comprise both the costs from NHS and PSS perspective and patients and informal carers perspective, and benefits received.

4.1.1 Intervention and comparator costs

4.1.1.1 Intervention costs

Intervention costs include costs of training and costs of delivery. The relevant cost components and intervention delivery were recorded by the research team alongside the progress of the trial.

The therapists who deliver the intervention are mental health professionals with appropriate post-qualification CBT training (BABCP accreditation) or equivalent experience. They were trained in different groups as sites opened at different times. The CBT therapists are considered as Band 7 staff. The training was delivered over 4 weeks in the one month before therapy delivery. They were provided with training manuals and Standard Operation Procedures (SOPs). During the study, therapists received weekly supervision from an experienced therapist. The time spent by staff on training and supervision were recorded by the research team. The opportunity costs of staff time will be estimated by multiplying the time and their salary + oncosts. The printing and posting expenses of training materials, the costs of venues and refreshments were recorded by the research team where applicable. It should be noted that the training was both for the study and the intervention. We will attempt to extract the training time relevant to the intervention only. Failing that, we will include all time spent following a conservative approach.

The intervention delivery comprises 9 therapist-led sessions and up to 3 additional sessions if deemed clinically appropriate by the therapist. The first session takes place face-to-face via video call for up to 90 minutes. A handout that summarises policies regarding confidentiality, cancelling or rescheduling sessions, contacting the therapist between sessions, safety, contact for technical queries, and downloading materials from the platform, is given to participants. The subsequent sessions take 50 minutes via instant messaging/typing on the INTERACT platform. The scheduled sessions are recorded on the INTERACT platform. While some sessions might last longer or shorter than 50 minutes, the exact duration is not recorded. We will therefore use the standard 50 minutes and Band 7 salary plus oncosts to estimate the opportunity costs of therapists' time. Printing costs of the handout were recorded if applicable.

The INTERACT platform is an online collaborative workspace for patient and therapist to communicate in real time and CBT worksheets and other materials are embedded within the platform. It was designed and developed as part of the NIHR-funded INTERACT programme of research. We therefore will not include the development costs of the platform in current

analysis. However, we will extract information from the research team records on the operating costs of the platform.

4.1.1.2 Comparator costs

Usual care comprises treatment as usual from GP, including referral to local psychological services provided by NHS Talking Therapy services (formerly IAPT) or prescriptions of antidepressant medication. No restrictions are applied on treatment options for usual care. The use of psychological therapy through NHS Talking Therapy services or privately was collected as part of the follow-up questionnaire at all follow-up points. A set of national average unit costs of the services will be compiled from published secondary sources of the appropriate year (2-4) and applied to the quantities collected to estimate the costs of usual care.

It should be noted that both groups can receive usual care from GP. The participants in the intervention group might also incur usual care costs.

4.1.2 Healthcare and social services costs for mental health

Data on healthcare services used are collected from two sources: general practice records and participants' self-reported questionnaires.

We will extract primary care consultations and prescribed medication for mental health from general practice records over the 12-month period post-randomisation according to the date of randomisation of participants at the end of 12 months period. For participants who do not consent to access to general practice records, we will use information on their use of medication reported on follow-up questionnaires at 3-, 6-, 9- and 12-months post-randomisation. For those who withdraw before 12 months post-randomisation, general practice records will not be accessed, the self-reported questionnaires up to the point of withdrawal will be used, unless they make specific request not to use any of their data. However, in the event of no consent or withdrawal, the primary consultation information will be considered missing.

The resource use questionnaire is administered as part of the CRF at 6- and 12-months post-randomisation. The items collected are: cCBT, counselling or talking therapies, community healthcare services, social services, NHS 111, NHS emergency services, and NHS hospital services. The providers of certain services are asked so that privately funded ones could be

separated and included in participants' spending or societal costs. Only the services funded by NHS and PSS will be included under healthcare and social services for mental health.

4.1.3 Participants' out-of-pocket spending

Participants' spending on private therapies or alternative treatments, home care, private hospital or clinic, over-the-counter remedies, and travelling expenses to GP appointments/treatments are collected in monetary terms as a part of the CRF at 6- and 12-months post-randomisation. Participants report as well if they are exempted from prescription charges at 6- and 12-months post-randomisation. The prescription charge will be estimated as £9.65 per item (5) and prescribed items will be identified from general practice records. It should be noted that this is a conservative approach as NHS offers 3-month and 12-month prescription prepayment certificates that might reduce the prescription charge spending.

4.1.4 Participants and/or informal carers' lost income

Participants' lost income due to mental health are collected in the CRF at 6- and 12-months in monetary terms. Because the questionnaires are completed by participants rather than informal carers, informal carers' lost income could not be collected directly. Instead, we collect informal carers' time off work due to caring for participants and their occupations. Their lost income will be estimated by multiplying the time by the average wages of their respective occupation categories (6, 7). It should be noted that informal carers' lost income is likely to be overestimated as they might take paid leave to care for participants. However, due to the difficulty of data collection, we will follow the conservative approach in the base case analysis and assume these days' income lost.

4.1.5 Benefits

Some healthcare and social services might be provided by employers or voluntary organisations to participants. These costs will be estimated using market prices of similar services. Participants might take paid leave from work for mental health, which will be considered one form of benefits as well. Paid time off due to mental health will be determined if participants take time off paid work but report not losing income. We also ask participants to report how their paid work is covered in their absence. Where temporary employment of personnel is reported and the leave taken is paid, this will be considered as benefits from employer to retain participant's job. Costs of paid leave will be estimated only for those reporting employment status as full-time worker or part-time worker. The average income of full-time and part-time employment will be applied to their days of paid leave to

estimate the costs of paid leave due to mental health (6). We are aware that this approach might produce overestimated costs of paid leave as the distribution of salary could be skewed.

Some participants are exempted from prescription charge. These are considered as another form of benefits and the exemption are recorded as part of the CRF at 6- and 12-months post-randomisation. The costs of this benefits will be estimated using identified prescribed items from general practice records and £9.65 per item charge (5).

We ask participants to report if their informal carers receive carer's allowance at 6- and 12-months post-randomisation. The published government allowance in the year consistent with other costing year will be used to estimate the costs of this benefit, which is £76.75 per week in 2023 (8).

4.2 Effectiveness measures

4.2.1 Quality-Adjusted Life Years

EuroQoL 5 domains with 5 levels (EQ-5D-5L) (9) is administered as a part of CRF at baseline, 6- and 12- months post-randomisation. The complete responses of the five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) will be used to convert to index values. Using area under the curve approach (10), the index values at the three time points will be used to derive quality-adjusted life years (QALYs). Following the recommendation by NICE (11), the mapping approach will used to execute the conversion of domains to index values (12).

5 ANALYSIS

5.1 Methods overview

All analyses will be carried out following an intention-to treat principle. We will attempt to present all monetary outcomes in pound sterling 2023, provided all public sources of service use are available at the time of analysis. If by the time of analysis, data of year 2023 remain unavailable, all monetary outcomes will be presented in pound sterling 2022. Discounting is not undertaken as the costs and outcomes cover a period of one year only.

We will use Excel for data compilation of intervention costs and data from general practice records. The resulting dataset will be merged with data from CRF and analysed using STATA MP18.0 or later version if available.

The descriptive statistics of the data will be presented by time point and group. The missing data pattern will be examined at this stage. Missing data will be handled primarily using multiple imputation on the assumption of missing at random. We will conduct within-trial incremental cost-effectiveness analyses of delivering the integrated approach to delivering CBT over and above usual care following the three perspectives of costs, of which the primary analysis will be from the NHS and PSS perspective (11).

5.2 Missing data

Missing data level will be described for all measures at all time points by groups and overall. Missing data pattern will be described accordingly.

Missing values at baseline assessment is expected to be rare and unrelated to the treatment allocation. These missing values will be imputed by the mean of the measure of the pooled sample of both groups (13). Missing data on measures at follow-ups will be handled following the framework outlined by Faria et al (14).

The association of missingness of each measure with group allocation and baseline covariates, and with observed values of the same measure at other follow-up points will be examined using statistical tests (univariate logistic regression for continuous and binary variables, χ^2 tests for discrete variables) with 0.05 as significant level. Missing values on measures at follow-ups will be handled using multiple imputation with chained equation method, following Rubin's rule and assuming missing at random (MAR) (15). An imputation model will be developed, including all the measures necessary to the analysis or associated with missingness identified by the statistical tests. The number of imputed datasets will be set as approximately the highest percentage figure of the missing data (13). The imputation will be performed by allocation groups.

All analyses will be conducted on the imputed dataset, unless otherwise specified.

5.3 Primary analysis

The primary analysis will be an incremental cost-utility analysis of integrated therapist and online CBT over and above usual care over 12 months from an NHS and PSS perspective.

Total costs include costs of intervention and usual care, costs of NHS/PSS healthcare, community care and social services for mental health. The effectiveness measure is QALYs over 12 months. Both incremental costs and incremental QALYs will be estimated using linear regression, adjusting for stratification (centre) and minimisation (gender, current antidepressant use, and BDI-II tertiles) variables. In addition, age and previous psychiatry referral will be added for further adjustment. Age is selected as one of the key demographic variables. Previous psychiatry referral serve as an indicator of past healthcare service use as this was not collected directly at baseline. Incremental QALYs will be further adjusted by index value at baseline. The incremental cost-effectiveness ratio (ICER) will be calculated by dividing the incremental costs by incremental QALYs, when both are positive.

Uncertainty around the point estimate will be assessed using non-parametric bootstrap re-sampling technique (16). Bootstrapping is an efficient method for calculating the confidence limits for incremental costs and QALYs, as its validity does not depend upon any specific form of underlying distribution. We will use bootstrap to generate 5,000 replicates of the sample with replacement to create a distribution for incremental costs and QALYs respectively. The 95% CIs for incremental costs and QALYs based on the bootstrapping results will be derived using the 2.5th and 97.5th percentiles of the respective distribution. A cost-effectiveness plane will plot 5,000 pairs of incremental costs and incremental QALYs on to a plane with four quadrants indicating four scenarios of cost-effectiveness (more costly more effective, more costly less effective, less costly more effective, less costly less effective). Dots fall on the quadrant indicating less costly more effective and on the quadrants indicating more costly more effective and less costly less effective but on the right side of the maximum acceptable ICER thresholds will show the uncertainty of cost-effectiveness of integrated therapist and online CBT over and above usual care. Cost-effectiveness acceptability curves (CEACs) (17) will be constructed based on the bootstrap iterations to estimate the probability that integrated therapist and online CBT is cost-effective at different threshold values, over and above usual care.

5.4 Secondary analysis

5.4.1 Cost-effectiveness analysis from participants' and informal carers' perspective

The cost-effectiveness analysis from participants' and informal carers' perspective will follow the same methods as the primary analysis. The costs of this analysis include participants' out-

of-pocket spending and participants' and/or informal carers' lost income. The incremental spending will be estimated by linear regression, adjusting for stratification (centre) and minimisation variables (gender, current use of antidepressant, and BDI-II tertiles), and other baseline covariates (age, history of depression, and employment status). The outcome measure is QALYs, same as in the primary analysis. The ICER and uncertainties will be estimated following the same approach as in the primary analysis. However, as there is no recommended maximum ICER thresholds from participants' and informal carers' perspective, the results will be described but not compared with any thresholds.

5.4.2 Cost-effectiveness analysis from societal perspective

Cost-effectiveness analysis from societal perspective will follow the methods of the primary analysis. The societal costs include the costs from NHS and PSS perspective and from participants' and informal carers' perspective, and benefits received. However, the prescription charges paid by participants and the exempted prescription charges as benefits to participants will be excluded from societal perspective as they reflect the money transfer among society rather than real consumption. If participants pay for treatments/services provided by employers and voluntary organisations, this spending will not be included to avoid double counting with estimated benefits. The incremental societal costs will be estimated using linear regression, adjusting for stratification (centre) and minimisation variables (gender, current use of antidepressant, and BDI-II tertiles), and other baseline covariates (age, history of depression, and employment status). QALYs are the primary outcome measure for this analysis. The ICER and uncertainties will be estimated following the same approach as in the primary analysis. Similar to the other secondary analysis, there are no recommended maximum ICER thresholds from the societal perspective. We will therefore only present the results. Unless the integrated therapist and online CBT shows higher probability of being both less costly and more effective over and above usual care, conclusions surrounding cost-effectiveness will not be drawn.

5.5 Sensitivity analyses

A series of sensitivity analyses will be undertaken to assess the uncertainties of the conclusion. To assess the impact of missing data, complete case analyses will be undertaken following the same approach of the base case analyses from the three perspectives but only on those who have complete data on costs, QALYs and baseline covariates. It is likely that

the number of participants included in the complete case analysis will be different between perspectives. As the wider the perspective goes, the less complete the data will be.

To examine the MAR assumption, sensitivity analyses will be carried out using pattern mixture modelling (14). This method assumes that data are missing not at random and sets rules for imputing to reflect this assumption. In the current analysis, we will assume that those who have missing values at follow-ups either are in need of more health care services or experience worse health, or both at the same time. To examine how these scenarios will affect the results based on MAR assumption, the incremental costs (or spending) and QALYs will be re-estimated based on data with 1) imputed costs (or spendings) are increased by 10%, 20% and 30%; 2) imputed QALYs are reduced by 10%, 20% and 30%; 3) the combination of 1) and 2).

6 SIGNATURES OF APPROVAL

Trial health economist: Jinshuo Li

Signature: _____ Date: _04/01/2024_____

Senior health economist: Steve Parrott

Signature: _____ Date: _04/01/2024_____

Chief investigator: Professor Nicola Wiles

Signature: _____ Date: __18/01/2024_____

7 REFERENCES

1. Tallon D, Thomas L, Brabyn S, Ching BCF, Hahn JS, Jude B, et al. Integrated therapist and online CBT for depression in primary care (INTERACT): study protocol for a multi-centre randomised controlled trial. *Trials*. 2023;24(1):421.
2. Jones K, H. W, Birch S, Castelli A, Chalkley M, Dargan A, et al. Unit Costs of Health and Social Care 2022. 2022.
3. NHS England, NHS Improvement. National Cost Collection 2021/22. National Cost Collection for the NHS2023.
4. NHS Business Services Authority. Prescription Cost Analysis - England 2021/22. 2022 9th June.
5. NHS. NHS Prescription charges 2021 [updated 31 March 2021. Available from: <https://www.nhs.uk/nhs-services/prescriptions-and-pharmacies/nhs-prescription-charges/>.
6. Office for National Statistics (ONS). Annual Survey of Hours and Earnings (ASHE) methodology and guidance 2023 [updated Jan 18. Available from: <https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/methodologies/annualsurveyofhoursandearningsashemethodologyandguidance>.
7. Office for National Statistics. Standard Occupational Classification (SOC) 2020 [updated 19 Jan 2023. Available from: <https://www.ons.gov.uk/methodology/classificationsandstandards/standardoccupationalclassifications/oc/soc2020>.
8. UK Gov. Carer's Allowance 2023 [Available from: <https://www.gov.uk/carers-allowance>.
9. EuroQol Research Foundation. EQ-5D-5L User Guide: Basic information on how to use the EQ-5D-5L instrument (version 3.0)2019 17/06/2020. Available from: Available at: <https://euroqol.org/publications/user-guides/>.
10. Richardson G, Manca A. Calculation of quality adjusted life years in the published literature: a review of methodology and transparency. *Health Econ*. 2004;13(12):1203-10.
11. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual (PMG36). In: Process and Methods, editor.: National Institute for Health and Care Excellence; 2022. p. 196.
12. Hernandez Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. *Pharmacoeconomics*. 2023;41(2):199-207.
13. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in medicine*. 2011;30(4):377-99.
14. Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *Pharmacoeconomics*. 2014;32(12):1157-70.
15. Rubin DB. Statistical Matching Using File Concatenation with Adjusted Weights and Multiple Imputations. *Journal of Business & Economic Statistics*. 1986;4(1):87-94.
16. Severens JL, De Boo TM, Konst EM. Uncertainty of incremental cost-effectiveness ratios. A comparison of Fieller and bootstrap confidence intervals. *International journal of technology assessment in health care*. 1999;15(3):608-14.
17. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ*. 2001;10(8):779-87.