ComBAT RCT

Community-Based Behavioural Activation Training (ComBAT) for Depression in Adolescents: Randomised Controlled Trial (RCT) with Economic and Process Evaluations and embedded feasibility testing

HEALTH ECONOMICS ANALYSIS PLAN

Version 1.0

York Trials Unit
Department of Health Sciences
University of York
York, YO10 5DD

Version date: 30 Oct. 24

Author(s): Jinshuo Li, Steve Parrott
Chief Investigator: Professor Lina Gega
Research Programme Manager: Dr. Lucy Tindall

Contents

1 REVISIONS

Version	Date	Summary of changes
0.5	30 Nov. 23	Initial draft
1.0	30 Oct. 24	Finalised version

2 GENERAL

2.1 Document scope

The current document describes the planned analyses of economic evaluation alongside the ComBAT randomised controlled trial (RCT).

This analysis plan has been checked for consistency with the ComBAT RCT trial protocol v4 (25 Sept 2023).

2.2 Glossary

AIC	Akaike Information Criterion
BA	Behavioural activation
BIC	Bayesian Information Criterion
CAMHS	Child and adolescent mental health services
CBT	Cognitive behavioural therapy
CCA	Cost consequence analysis
CDRS-R	Children's depression rating scale - revised
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curves
CHU-9D	Child health utility – 9 dimensions
ComBAT	Community-based behavioural activation training

CWP	Children's wellbeing practitioner
CYP IAPT	Children and young people's improving access to psychological therapies
IAPT	Improving access to psychological therapies
ICER	Incremental cost-effectiveness ratio
IPT	Interpersonal therapy
LA	Local authority
MAR	Missing At Random
MI	Multiple imputation
MNAR	Missing Not At Random
MOOC	Massive open online courses
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PHQ-9A	Patient Health Questionnaire – Modified for Adolescents
PSS	Personal Social Service
QALY	Quality-adjusted Life Year
RCT	Randomised controlled trial
RCADS	Revised Childrens' Anxiety and Depression Scale
RUQ-A	Resource utilisation questionnaire for adolescents
SAP	Statistical analysis plan
YTU	York Trials Unit

3 TRIAL SUMMARY

The following sections briefly describe the ComBAT RCT. For full details please see the protocol (v4, 25/09/2023).

3.1 Aim and objectives

The aim of the economic evaluation is to establish the cost-consequences of a community-based behavioural activation training (ComBAT) for depression in adolescents compared with usual care.

Specific objectives are:

- To describe the components and estimate the costs of ComBAT;
- To assess the impact of ComBAT on entry to Child and Adolescent Mental Health Services (CAMHS) compared to usual care at 6 and 12 months post-randomisation;
- To conduct a cost-consequence analysis of ComBAT compared with usual care for the National Health Service (NHS) and Personal and Social Service (PSS) and for the education sector;
- To conduct an incremental cost-effectiveness analysis of ComBAT compared with usual care from the mental health service perspective at 6 months post-randomisation (primary outcome timepoint).

3.2 Design

The ComBAT RCT is a parallel two-group randomised controlled trial with allocation at the level of individual. The trial is being delivered in a variety of services responsible for providing support to young people with mild to moderate depression. These include NHS services such as CAMHS, school-based or other community-based services. These sites are involved in the identification of study participants and are the locations for intervention delivery.

The inclusion criteria of participants are: 1) aged 12-18 years at the date of consent; 2) score ≥65 on the depression subscale (10-items) of the Brief version of the Revised Children's Anxiety and Depression Scale (RCADS); 3) scores <15 on the Patient Health Questionnaire – Modified for Adolescents (PHQ-9A); 4) provide consent, or assent along with their parent's consent (if applicable), to participate in the study.

The PHQ-9A is being used to screen for depression severity and suicide risk. If a young person scores ⩾15 in the sum of the 9 items (indicating severe depression), or responds "more than half-days" or "nearly every day" on question 9 and/or yes to SQ3 and SQ4, they will be invited to speak with a clinical member of the ComBAT team to confirm their eligibility for entry to the study, or be signposted to other services as necessary.

Participants are excluded if they have severe depression or an increased risk of suicide; meet criteria for secondary care (tier 3/high intensity therapy) for reasons other than risk of suicide or severity of the depressive symptoms, such as a learning disability or complex comorbid conditions; cannot speak English and do not have a carer or other designated adult to translate the intervention and research materials, and to translate conversations during sessions with a professional.

The sample size is set at 236. Participants are randomised to either group at 1:1 ratio, using simple randomisation. Randomisation is implemented using a web-based system designed and developed by the data management team at York Trials Unit (YTU).

After baseline, follow-ups are conducted at 6- and 12-months post-randomisation. The measures related to the economic evaluation are presented in the following section. For a detailed schedule of all measures please see protocol (V4; 25/09/2023).

4 OUTCOMES AND DATA COLLECTION

4.1 Costs

As ComBAT may impact multiple stakeholders beyond the health care system, the costs include those incurred by the NHS/PSS and by non-NHS/PSS organisations and society in general.

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 service use will be recorded by the research team alongside the progress of the trial to support a bottom-up approach.

The training of ComBAT support workers is arranged with sites at an appropriate time and location. It is planned to take 6 hours and delivered in one day by members of the study team. The number of trainers is selected relative to the number of attendees. As the sites are recruited and open at different times, the training has to be delivered separately on several occasions in person or online. The training manual and role play explanations are given to attendees in hard copy or via email. The fees of training venue, refreshments, printing and transportation are recorded as they occur.

The attendees are encouraged to complete, before or after the training, the online MOOC course: The Introduction to Behavioural Activation for Depression (https://www.futurelearn.com/courses/introduction-to-behavioural-activation-for-depression), which was developed by the study team and is free of charge. The MOOC course is designed to be completed over 3 weeks, with study time of 4 hours per week. The MOOC is hosted on the FutureLearn platform, the subscription of which is covered by University of York as an organisation. It is therefore free of charge for individual course developers within the University. There is no licence fee required for any part of the content. The course was produced previously during the feasibility study stage, no further costs were incurred thereafter.

After the initial training, attendees will be encouraged to take up supervision as much as they would like to. The supervision will be held in both group and individual formats, according to attendees' preferences. Two clinical members of the study team will act as supervisors. Supervision sessions are expected to take approximately one hour per session, regardless of whether they are delivered to an individual or group. Refresher training will be provided if necessary. These sessions will be recorded as they occur.

The intervention delivery is organised in 5 modules which can be completed in up to 8 weekly sessions of 30-40 minutes each in a blended model of professional-guided sessions and self-directed activities. The participants are encouraged to keep a log of each activity that they complete.

All other costs will be estimated based on the study team records. The opportunity costs of time for both trainers and the ComBAT support workers will be estimated by multiplying their respective hourly costs by the time they spent on the training. The hourly costs of trainers and ComBAT support workers will be identified by recording their wage bands or professional roles, plus associated salary oncosts, and overheads. As our rationale behind the study is that BA could be delivered by professionals who are less expensive to employ, the expected pay level of ComBAT support workers is below NHS pay grade 7 or non-NHS equivalent. Depending on the organisation and its locality, the ComBAT support workers may be a mixture of NHS and non-NHS employees.

4.1.1.2 Comparator costs

The comparison group in the ComBAT RCT is usual care. Usual practice for child and adolescent mental health can be widely varied and inconsistent. It may be no intervention,

signposting to alternative sources of support, general discussion, supportive counselling, relaxation, recreation groups, guided self-help or psychological therapies including CBT and IPT. Professionals involved in usual care, in turn, vary greatly by support/treatment as well as from one service to another.

We therefore do not pre-specify a standard usual care. Instead, participating professionals in the usual care arm are asked to complete a session record at each session to outline what approaches they have taken. Where usual care involves signposting young people to external support, professionals are asked to provide information about this (i.e. where the young person was signposted to).

A set of national average unit costs of the support/treatment options will be compiled from published secondary sources of the appropriate year (1-3) and applied to the quantities collected to estimate the costs of usual care.

4.1.2 Healthcare, community, social and school services costs

Healthcare services use is collected using a bespoke self-reported resource use questionnaire for adolescents (RUQ-A). The RUQ-A is administered as part of the case report form (CRF) to the participants at baseline, 6- and 12-months post randomisation.

The services in public sectors included are: general health and community services (GP, practice nurse, community paediatrician, NHS 111 call, NHS Walk-in centre, health visitor, children's centre, social worker/family support worker, online or telephone counselling), school services (teacher, school nurse, school counsellor), CAMHS (psychiatrist, psychological therapist, psychologist, mental health nurse, family therapist), and NHS hospital services (Accident & Emergency/Urgent care, inpatient ward, outpatient clinic). For all the service categories we allow an open question for participants to provide additional services within the category they use. We also collected name, dose, and start/end date of any medications taken for mental health.

A set of national average unit costs of the listed services will be extracted from published secondary sources of the appropriate year (1-3) and applied to the quantities collected to estimate the costs of healthcare and community services for mental health.

The services in the private sector are not pre-specified. Participants are asked about the name, number of uses and the amount paid for the services they have used.

4.2 Effectiveness measures

Multiple effectiveness measures are collected to provide meaningful results for different stakeholders. All measures are administered as part of the CRF at baseline, 6- and 12-months post-randomisation.

4.2.1 Revised Children's Anxiety and Depression Scale (RCADS) – Brief Version – 25 items

The primary outcome of the ComBAT RCT is depressive symptoms measured by RCADS at 6 months post-randomisation. The RCADS brief version is a 25-item questionnaire that assesses children's depression and anxiety, which is a condensed version of the original 47-item (4) and has been validated as a self-completed outcome measure for 8-to-18-year-olds. Both versions of the RCADS have sub-scales that capture symptoms in 6 domains: depression, generalised anxiety disorder, panic disorder, obsessive compulsive disorder, separation anxiety disorder and social anxiety. All items are rated on a 4-point Likert-scale from 0 to 3 (0 = Never, 1 = Sometimes, 2 = Often, and 3 = Always). Raw scores are transformed into t-scores by matching the raw score to its corresponding age and gender normed t-scores (available on the measure's website https://www.childfirst.ucla.edu/resources/). Higher t-scores denote greater clinical need. Clinical cut-offs for the t-scores are: 0-64 non-clinical range, 65-69 borderline clinical range, and ≥70 clinical range.

4.2.2 Quality-Adjusted Life Years

The Child Health Utility – 9 Dimensions (CHU-9D) (5) is used to derive health gain in quality-adjusted life years (QALYs). The questionnaire consists of 9 domains, each with 5 statements (scored 1–5) that assess the young person's functioning "today" across domains of worry, sadness, pain, tiredness, annoyance, school, sleep, daily routine and activities. For example: 1= I don't feel sad today, 2=I feel a little bit sad today, 3=I feel a bit sad today, 4=I feel quite sad today, 5=I feel very sad today. The responses under the 9 domains can be taken together as a description of the young person's "health state" that combines all responses across all items (e.g. 11232152). Different utility weights are assigned to each level of each domain. Different combinations of responses across the 9 dimensions therefore result in different health states that have a utility value on a 0–1 scale, where 1 is perfect health and 0 is equivalent to being dead. The UK young people valuation set will be used to derive the utility values (6).

4.2.3 Days absent from school, training or work

The RUQ-A also includes questions about participants' days absent from school, training or work due to health worries, and days of work that their family members have taken to look after them. These would not be quantified in monetary terms.

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 2024, provided all public sources of service use are available at the time of analysis. If by the time of analysis, data of year 2024 remain unavailable, all monetary outcomes will be presented in pound sterling 2023. 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 and usual care costs. The resulting dataset will be merged with data from the CRFs and cleaned using the latest available version of Stata. The descriptive statistics will be generated in Stata. The multi-level regression analysis will be conducted using MLwiN 3.14 (7).

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 (see 5.2 below). We will carry out a cost-consequence analysis (CCA) of the ComBAT intervention compared to usual care due to the multiplicity of stakeholders and the need to present a comprehensive picture of costs and consequences from different perspectives. We will also conduct a within-trial incremental cost-utility analysis from the NHS and PSS perspective (8).

5.2 Missing data

Missing data level will be described for all measures at all time points by groups and in total. Missing data patterns will be described accordingly.

Missing data will be handled based on the framework proposed by Faria et al (9). Missing values of baseline data are expected to be rare and unrelated to the group allocation. These missing values will be imputed by the mean of the measure of the pooled sample of both groups (10).

Missing values of data at follow-ups will be handled using multiple imputation with chained equation method, following Rubin's rule and assuming missing at random (MAR) (11). 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. An imputation model will be developed, including all the measures necessary for the analysis or associated with missingness identified by the statistical tests. The number of imputation will be set as approximately the highest percentage figure of the missing data (10). 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 a cost-consequence analysis (CCA) of ComBAT compared to usual care over 12 months from NHS/PSS perspective and the education perspective.

Total costs include costs of intervention and usual care, and costs of healthcare, school-based care, community care and social services for mental health over 12 months. The costs from NHS/PSS perspective and from the education perspective will be presented both separately and in total. The effectiveness measures are QALYs and number of days absent from school/work/training over 12 months. Both incremental costs and incremental QALYs will be estimated using linear regression, adjusting for costs and utility values at baseline respectively and other baseline covariates that show a significant association ($p<0.05$) with dependent variables. The difference in number of absent days will be estimated similarly, using linear regression. The appropriate models will be selected based on AIC and BIC information criteria. A Likelihood Ratio test will be used to indicate if random effects should be considered. The incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the incremental costs by incremental outcomes, when both are positive.

Uncertainty around the point estimate will be assessed using the non-parametric bootstrap re-sampling technique (12). Bootstrapping is an efficient method for calculating the confidence limits for variables possibly deviating from normality, as its validity does not depend upon any specific form of underlying distribution. We will use bootstrapping to generate 5,000 replicates of the sample with replacement to create a distribution for incremental costs and outcomes. The 95% CIs for incremental costs and outcomes based on the bootstrapping

results will be derived using the 2.5th and 97.5th percentiles of their respective distribution. Multiple cost-effectiveness planes will be plotted using 5,000 pairs of incremental costs and corresponding incremental outcomes 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). Cost-effectiveness acceptability curves (CEACs) (13) will be constructed based on the bootstrap iterations to estimate the probability that ComBAT is cost-effective at different threshold values, compared to usual care. Incremental costs per QALY gained from NHS/PSS perspective will be compared with the maximum acceptable threshold of ICER recommended by NICE (8). No official thresholds are available from education perspective so no conclusion will be drawn.

5.4 Secondary analyses

We will undertake incremental cost-effectiveness analyses from mental health service perspective as secondary analyses. The outcome measure of secondary analyses was based on RCADS t-score.

First, we will use the RCADS t-score directly as in the clinical effectiveness analysis. The difference in RCADS t-score at 6 months (primary endpoint) will be estimated following the statistical analysis, using a mixed-effects generalised linear regression model. The model will adjust for RCADS at baseline and include trial group, group-by-time interaction and other baseline covariates as fixed effects, and participants and therapists as random effects to account for repeated measures within participants and possible clustering by therapist.

Secondly, we will calculate the reliable change index (RCI) for RCADS t-score, using standard deviation and Cronbach's α estimated from the pooled sample of both groups at baseline, along with 95% inclusion interval (Equation 1) (14, 15). The change is defined as reliable if the difference in RCADS t-scores between baseline and 6 months is larger than the estimated RCI, otherwise no reliable change. As lower t-scores on RCADS indicate better outcomes, the reliable change is referred to as reliable improvement when the change is deemed reliable and the score at 6 months is lower than at baseline.

Equation 1

$$RCI = SD \times \sqrt{2} \times \sqrt{(1 - Cronbach's\ \alpha)} \times 1.96$$

The proportion of participants who make reliable improvement in each group will be calculated. The difference between groups will be calculated by subtracting the proportion in the usual care group from the proportion in the ComBAT group.

The difference in costs of treatments (ComBAT and usual care) and other mental health specific services from baseline to 6 months follow-up will be estimated using generalised linear regression model.

These differences will be used to estimate the incremental costs of ComBAT, comparing with usual care, 1) to reduce one point on RCADS t-score, and 2) to achieve one case of reliable improvement by RCADS t-score.

5.5 Sensitivity analyses

A series of sensitivity analyses will be undertaken to assess the uncertainties of the conclusion. While the primary outcome is RCADS t-score, one of the eligibility criteria used RCADS depression subscale. We will therefore conduct a sensitivity analysis using RCADS depression subscale t-score for classification of non-clinical, borderline and clinical depression, instead of RCADS t-score.

To assess the impact of missing data, complete case analyses will be undertaken following the same approach of the primary analysis but only on those who have complete data on costs, QALYs, number of absent days and baseline covariates.

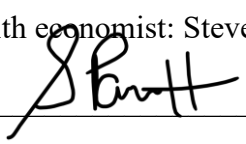
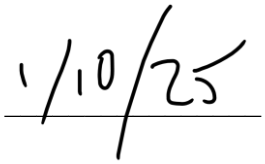
To examine the robustness of the MAR assumption, sensitivity analyses will be carried out using pattern mixture modelling (9). This method assumes that data are missing not at random (MNAR) and sets rules for imputing to reflect this assumption. In the current analysis, we will assume that those who have missing values at follow-ups either need more health care services or experience worse health (lower utility values and higher RCADS scores), or both at the same time. To examine how these scenarios will affect the results based on MAR assumption, the incremental costs and QALYs will be re-estimated based on data with 1) imputed costs are increased by 20%, 40% and 60%; 2) imputed QALYs are reduced by 20%, 40% and 60%; 3) imputed RCADS are increased by 20%, 40% and 60%; 4) the combination of 1) and 2); 5) the combination of 1) and 3).

6 SIGNATURES OF APPROVAL

Trial health economist: Jinshuo Li

Signature: _  _____Date: _30/09/2025_____

Senior health economist: Steve Parrott

Signature: _  _____Date: 

Programme manager: Dr Lucy Tindall

Signature: _  _Date: _02.10.2025_____

Chief investigator: Professor Lina Gega

Signature:  Date: 01/10/2025

7 REFERENCES

1. Jones K, H. W, Birch S, Castelli A, Chalkley M, Dargan A, et al. Unit Costs of Health and Social Care 2022. 2022.
2. NHS England, NHS Improvement. National Cost Collection 2021/22. National Cost Collection for the NHS2023.
3. NHS Business Services Authority. Prescription Cost Analysis - England 2021/22. 2022 9th June.
4. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: a revised child anxiety and depression scale. Behav Res Ther. 2000;38(8):835-55.
5. Stevens KJ. Working with children to develop dimensions for a preference-based, generic, pediatric, health-related quality-of-life measure. Qualitative health research. 2010;20(3):340-51.
6. Stevens K. Valuation of the Child Health Utility 9D Index. PharmacoEconomics. 2012;30(8):729-47.
7. Charlton C, Rashbash J, Browne WJ, Healy M, Cameron B. WLwiN Version 3.14. Centre for Multlevel Modelling, University of Bristol; 2025.
8. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual (PMG36): National Institute for Health and Care Excellence; 2022 [updated 31 Oct 2023. 196]. Available from: https://www.nice.org.uk/process/pmg36.
9. 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.
10. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Statistics in medicine. 2011;30(4):377-99.
11. Rubin DB. Statistical Matching Using File Concatenation with Adjusted Weights and Multiple Imputations. Journal of Business & Economic Statistics. 1986;4(1):87-94.
12. 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.
13. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Econ. 2001;10(8):779-87.
14. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. Journal of consulting and clinical psychology. 1991;59(1):12-9.
15. Evans C, Margison F, Barkham M. The contribution of reliable and clinically significant change methods to evidence-based mental health. Evidence Based Mental Health. 1998;1(3).