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Cognitive behavioural therapy versus standardised medical care for adults with dissociative non-epileptic seizures (CODES): statistical and economic analysis plan for a randomised controlled trial

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Abstract

Background: Dissociative seizures (DS), also called psychogenic ‘non-epileptic’ seizures, are a distressing and disabling problem for many patients in neurological settings with high and often unnecessary economic costs. The CODES Trial evaluates a specifically-tailored psychological intervention with the aim of reducing seizure frequency and severity, and improving psychological well-being in adults with DS. The aim of this paper is to report in detail the quantitative and economic analysis plan for the CODES Trial, as agreed by the Trial Steering Committee.

Methods: The CODES Trial is a multicentre, pragmatic parallel group randomised controlled trial (RCT) to evaluate the clinical and cost-effectiveness of 13 sessions of cognitive behavioural therapy (CBT) plus standardised medical care (SMC) in comparison to SMC alone for adult outpatients with DS.

Discussion: The objectives and design of the trial are summarised, and the aims and procedures of the planned analyses are illustrated. The proposed analysis plan addresses statistical considerations such as maintaining blinding, monitoring adherence with the protocol, describing aspects of treatment and dealing with missing data. The formal analysis approach for the primary and secondary outcomes is described, as well as the descriptive statistics that will be reported. This paper offers transparency to the planned inferential analyses for the CODES Trial, prior to the extraction of outcome data. It also provides an update to the previously published trial protocol and guidance to those conducting similar trials.

Trial Registration

ISRCTN registry ISRCTN05681227 (registered 05 March 2014); ClinicalTrials.gov NCT02325544 (registered 15 December 2014).

Keywords

Statistical Analysis Plan, CODES Trial, nonepileptic seizures, dissociative seizures, cognitive behavioural therapy, randomised controlled trial.
Background

CODES Trial

The CODES Trial is a multicentre, pragmatic parallel group randomised controlled trial (RCT) to evaluate the clinical and cost-effectiveness of 13 sessions of cognitive behavioural therapy (CBT) plus standardised medical care (SMC) in comparison to SMC alone in reducing dissociative seizure frequency and severity, and improving seizure freedom, quality of life, psychosocial well-being and cost effectiveness in terms of health service use in adults with dissociative (non-epileptic) seizures [1]. The protocol paper for the CODES Trial has been published previously [1]; and the aim of this paper is to report in detail the quantitative and health economic analysis plan, as agreed by the Trial Steering Committee in April 2016.

Dissociative Seizures

In the region of 12-20% of patients seen in epilepsy clinics may be having dissociative seizures (DS) rather than epileptic seizures[2] and rates of DS incidence have been estimated around 4.9/100,000/year[3]. Although DS are paroxysmal events that resemble epileptic seizures or syncope, they are not associated with ictal electroencephalographic (EEG) discharges. Other common names for DS include ‘psychogenic non-epileptic seizures’ and ‘non-epileptic attacks,’ and they are found under the umbrella headings of dissociative and conversion disorders in psychiatric classifications. DS presents a challenge for clinicians in terms of their diagnosis and management. DS patients demonstrate high rates of psychiatric comorbidity such as anxiety, depression and post-traumatic stress disorder[4] and it has been shown that they have a raised risk of mortality, unrelated to their seizures[5]. Patients with DS may go through expensive or unnecessary interventions, they can sustain injuries during a seizure, and their quality of life is lower than in epilepsy patients[6]. If a correct diagnosis is given, it has been shown that medical service use and costs can reduce[7].
Despite limited evidence to date for its effectiveness[8-12], psychotherapy is viewed as the
treatment of choice[13]; however, the involvement of psychiatrists and psychologists is variable.
NICE[14] and the Scottish Intercollegiate Guidelines Network (SIGN)[15] have recognised the need
for psychiatric and psychological input for DS patients, which would benefit from the development
of neuropsychiatry care pathways[16], i.e. bridging the gap between neurology and psychiatry.
However, there is little basis on which to recommend a particular type of psychotherapy for this
patient group and care provision in the UK remains extremely variable.

The CODES Trial will, therefore, permit evaluation of the clinical and cost effectiveness of Cognitive
Behavioural Therapy (CBT) specifically adapted for DS patients within a structured care pathway
involving neurology, liaison/neuropsychiatry and psychotherapy and should then provide a model
for future services and more rational commissioning of care for this patient group. It will provide a
basis for the wider training of therapists to work with DS patients and support the role of
psychiatrists in treating this group of patients, who commonly have complex mental health care
needs.

**Research objectives**

**Primary objective**
To evaluate the effectiveness of CBT (plus SMC) compared to SMC alone in reducing monthly
dissociative seizure frequency at 12 months post randomisation.

**Secondary objectives**
To evaluate the effectiveness of the intervention in terms of further secondary outcomes;
specifically to assess:
1. reductions in subjective DS severity and disability, and improvements in seizure freedom, psychosocial and psychological well-being and health-related quality of life following CBT plus SMC compared to SMC alone at 12 months post randomisation;

2. a reduction in health service use at 12 months post randomisation following CBT plus SMC compared to SMC alone; and

3. the cost effectiveness of CBT plus SMC compared to SMC alone at 12 months post randomisation.

In addition, the study seeks to characterise:

4. the global clinical improvement shown by patients as a result of either treatment; and

5. participants’ satisfaction with either treatment.

Outcome measures

The primary outcome measure is monthly DS frequency at 12 months post-randomisation, defined as seizure occurrence over the previous four weeks[1]. This will also be collected at 6 months post randomisation as an auxiliary variable (see explanation below). Seizure frequency data will be recorded by patients in daily seizure diaries and will be collected by the research workers every two weeks throughout the trial by whichever means patients find acceptable (diaries, text/phone/online). The research workers will then enter the data as weekly seizure counts into the database system (MACRO) set up for this trial by King’s Clinical Trials Unit (KCTU) at the Institute of Psychiatry, Psychology and Neuroscience (IoPPN) in London.

Monthly DS frequency will be converted into an incidence rate by the trial statistician. The incidence rate is defined as the number of seizures (count) divided by the number of days. The number of days will depend on how many weekly seizure counts are recorded for each participant at the follow-up time points (7, 14, 21 or 28 days). If the seizure diary has not been collected for the relevant four
weeks at 6 months (weeks 23-26) and 12 months (weeks 49-52) post randomisation, an allowance of
two weeks will be given either side of these time-points in order to calculate monthly seizure
frequency.

An overall self-report estimate of DS frequency in the preceding four weeks will also be requested
from participants at baseline, and at the two follow-up time points, to help deal with missing diary
data.

See Table 1 in the trial protocol [1] for further details of all outcome measures and assessment
timings.

**Trial Design**

The CODES trial is a multicentre, parallel group superiority RCT. It comprises a two stage screening
phase: an initial assessment is carried out at recruitment and a re-assessment at the psychiatrist visit
approximately three months later. Further information on this eligibility screening can be found in
the protocol[1] and an illustration of the screening, recruitment, randomisation and follow up
process is provided in Figure 1.

Once both phases of consent and baseline assessments are complete, the individuals are
randomised to one of the treatment arms. The procedure is as follows: on receipt of notification
that the patient has consented to the RCT and that the baseline questionnaires have been
completed, the local research worker electronically submits details of each participant to the KCTU
online randomisation system (www.ctu.co.uk/randomisation). This includes: participant ID number,
study centre, initials and date of birth. The system generates confirmation emails that can be blind
or unblind to treatment allocation. Therefore, relevant staff will be immediately notified of the
treatment allocation, with or without unblind details depending on their role in the study.
Specifically, the research workers will receive a blinded confirmation of successful randomisation, and the Trial Manager and Principal Investigator will receive an un-blinded notification. The CBT therapists delivering the manualised CBT will be informed of the details of the person randomised to that intervention by the Trial Manager and will liaise with patients to arrange their attendance at appointments.

7 Randomisation and Blinding

Randomisation is undertaken using a 1:1 ratio and is stratified by liaison/neuropsychiatry centre with variable block sizes within centres to ensure that the distribution of centres is balanced across the two trial arms. There are a total of 18 centres that are involved with patient randomisation.

Blinding is planned for outcome assessors (research workers) and the trial statistician. Evidence for unblinding of treatment to assessors will be studied to ascertain whether or not they could tell to which treatment arm the participants were randomly allocated for the trial; at 12 months or withdrawal, the assessors will guess the arm to which they think the participants were allocated. The trial statistician will then compare whether the proportion who guess CBT in each arm is different or not.

INSERT FIGURE 1 ABOUT HERE.

Sample size

Data from our pilot RCT study (comparing CBT and SMC on a comparable population) which was the largest study at the time informed our sample size calculations[11]. Analysis of seizure outcome in that study controlled for pre-randomisation seizure frequency, and found a large standardised effect size of Cohen’s d=0.75 [17] (log scale) for seizure frequency reduction following CBT in comparison to SMC at the end of CBT treatment (measured at a comparable time point for the SMC group). Of
relevance for the calculation of the CODES sample size, our earlier study also yielded a moderate
effect size of Cohen’s d=0.42 (log scale) 6 months after the end of treatment, which broadly
approximates the 12 month post randomisation follow up point in CODES. We therefore based our
sample size estimation on this moderate effect size which we considered to be clinically meaningful.

We were also able to consider effect sizes for other non-seizure related outcomes. We found that in
other studies of CBT-based psychotherapy for functional symptoms, it is not uncommon to obtain
moderate effect sizes. For example, a large RCT studying patients with Chronic Fatigue Syndrome
that permitted a comparison between CBT and standard medical care yielded a standardised effect
size of d >0.5 at 52 weeks post randomisation[18]. An RCT study of a brief guided self-help CBT
approach for patients with a mixture of functional neurological symptoms (10% of whom had DS)
yielded an effect size of d=0.48 at 3 months[19]. Thus, we are aiming to be able to detect an effect
size comparable to that found in other CBT-based interventions with patients with
functional/medically unexplained symptoms.

An initial calculation suggested that 121 participants were needed per group to detect an effect size
of d=0.42 with 90% power at the 5% significance level using a 2-sided t-test for log-frequencies.
However, this number needed to be inflated to allow for therapist effects within the CBT group.
Therefore, by using an intraclass correlation coefficient (ICC) of 0.02 which is based on a typical
therapist ICC [20], and assuming that around 15 therapists will be delivering CBT, the sample size
increased to 149 participants per arm which would achieve 92.6% power (using the cluspower
command in Stata allowing for clustering in only one trial arm).

As explained further in the inferential analysis section below, pre-randomisation seizure frequency
will be recorded for all of the participants and included as a covariate in the analysis model. This
means that the precision of future intervention effect estimates will increase, and so to account for
this we applied a deflation factor of 0.83 which is based on a correlation between pre-randomisation and follow-up in frequencies of $r=0.42^{[21]}$. Finally, attrition needed to be accounted for to re-inflate the sample size. In the pilot RCT 11% patients were lost to follow-up$^{[11]}$ but we allowed for a more conservative attrition rate of 17% at 12 months. Therefore, our final sample size to aim for is 149 participants per arm; a total of 298 participants.

Treatment duration and timing of outcome assessments

CBT therapists who have undergone further specific training for the CODES trial will deliver 12 sessions of CBT +1 booster session. CBT will take place over 4 to 5 months with a further booster session approximately 9 months after randomisation.

All participants will complete follow up measures at two time-points: 6 and 12 months post randomisation. The aim is for follow-up assessments to be collected up to 4 weeks before and up to 8 weeks after the two time-points, where outcomes can be considered reasonably constant. If a large proportion of outcome data is collected outside this stability window then sensitivity analysis will be considered to adjust for the time difference.

Participants randomised to SMC alone will be referred for psychotherapy if they are deemed clinically to require this at the end of the study and after the 12 month follow-up is complete, but no further data will then be collected on these people and this treatment course will not form part of the clinical trial.

Auxiliary information

As explained above, the primary outcome is seizure frequency at 12 months post randomisation as recorded in patient seizure diaries. We also collect further reports of seizure frequency: seizure frequency at 6 months post randomisation and patient self-reported number of seizures in the last
four weeks. We will use such auxiliary information to assess the size of measurement error in our
primary outcome and also to predict missing values in the primary outcome analysis (see multiple
imputation process below). Regarding measurement precision, Cohen's Kappa statistic and
Spearman’s rank correlation coefficients will be calculated to assess inter-measurement method
reliability and the strength of any monotonic relationship.

Data analysis plan

Baseline comparability of randomised groups

Baseline descriptions of participants by treatment and overall will be provided: minimums and
maximums, means and standard deviation, medians and quartiles for continuous variables as
appropriate. Frequencies and proportions will be presented for categorical variables. No significance
testing will be used to test baseline differences between the trial arms. All baseline variables will be
reported overall and by trial arm. These will be grouped into participant demographics and
participant clinical information. The primary and secondary outcomes will also be summarised
overall and by trial arm.

Adherence to allocated treatment

Within the CBT arm, adherence to allocated treatment will be described using study-specific therapy
logs, completed by the CBT therapists. These will record attendance at CBT sessions or reasons for
non-attendance as well as rate completion of homework tasks and implementation of activities
negotiated in sessions, and whether or not dissociative seizures experienced in session disrupted
therapy. Compliance (adherence) is defined as having attended at least 9 of the sessions of CBT. A
summary of the number of CBT sessions attended, and the number of patients compliant with CBT
sessions will be provided. Compliant versus non-compliant participants will be compared on baseline
variables; and the reasons for withdrawal from treatment will be summarised.
In addition, CBT sessions will be recorded with participants’ consent and a random selection of these audio recordings will be used to rate therapy integrity, to assess the extent to which therapists adhered to the study-specific CBT\[1\]. The number of participants in the SMC arm who received the active treatment component (CBT), i.e. treatment contamination, will be described. This will be compared against the health service use data in the economic analysis for consistency.

Lost to follow-up and other missing data

Withdrawal from trial follow-up (attrition rate) will be reported by intervention group. The proportions of participants with missing values for each variable will be summarised in each arm and at each time point. The reasons for withdrawal from the trial will be summarised.

The baseline characteristics of those missing 12 month follow up data will be compared to those with complete follow up. The relationship between baseline characteristics and missing data will also be investigated graphically. Imputation by chained equations (ICE), a form of multiple imputation (MI), will be used in the formal analysis to deal with missingness; and predictive baseline characteristics will be included in this process.

The relationship between drop-out from therapy and lost to follow-up will also be described. This will be performed by an independent statistician in order to remain blinding of the trial statistician. Binary variables will be constructed for completion of at least 9 CBT sessions (“compliant”) and for drop-out at 12 months. The relationship between these two post-randomisation variables within the CBT arm will be assessed by using a chi-squared test, and will inform the decision of whether to include this “compliance” variable in the ICE step, which is explained further in the inferential analysis section.

Adverse event reporting
Adverse events (AE), adverse reactions (AR), serious adverse events (SAE) and serious adverse reactions (SAR) will be summarised by trial arm and overall.

**Descriptive statistics for outcome measures**

Each of the primary and secondary outcome measures as listed in the protocol[1] will be described by treatment group and time point. Means and standard deviations or medians and interquartile ranges will be used for continuous variables, where relevant. We will check whether continuous outcomes can be assumed to be normally distributed using visual diagnostics, such as residual plots. Histograms and goodness of fit tests will be used to assess whether the count variables have a Poisson distribution; i.e. whether the variances equal the means or if there is evidence of over-dispersion. Frequencies and proportions will be used to describe categorical variables.

**Inferential analysis**

**Aims of formal inferences**

An intention to treat approach will be employed to estimate effectiveness: The formal statistical analyses will estimate the differences in relevant summaries (means, incidence rates) between patients randomised to CBT plus SMC and SMC alone at the various post-treatment observation time points. Group difference estimates and associated 95% confidence intervals will be reported. The significance level will be 5% (two-sided) for the primary outcome.

Missing post randomisation assessments will be dealt with by using the ICE approach for MI; provided that predictors of missingness are included in the ICE step, the analysis should remain valid in the presence of missing data under the missing at random (MAR) assumption. The trial statistician will remain blind until the main analyses have been completed. Any analyses that cannot be performed blind (e.g. modelling therapist effects in the CBT arm) will be done at the end of the analysis in order to preserve blindness for as long as possible.
Sensitivity analyses will be used to assess the robustness of conclusions to non-ignorable missing outcome data and to departures from randomised treatment.

**Analysis of the primary outcome**

The analysis population will include all patients who were randomised. The primary outcome is monthly seizure frequency at 12 months post randomisation, defined as seizure occurrence over the previous four weeks. For the purpose of the primary outcome analysis, this will be taken as measured by the seizure diaries. Other seizure variables will be included in the imputation step, as explained below.

Seizure frequency will be captured by a seizure count and an exposure period. An individual’s incidence rate is then defined by the number of seizures divided by number of days (7, 14, 21 or 28 days), as explained above. The frequency outcome will be modelled using generalised linear mixed modelling (GLMM) for Poisson data. The count outcome at 12 months will constitute the dependent variable and an offset will be used to acknowledge any variability in exposure periods. A Poisson model expresses the effect of the intervention in the form of an incidence rate ratio (IRR) contrasting the expected number of seizures under CBT plus SMC with the expected number under SMC alone.

The explanatory variables will be seizure frequency at baseline, randomisation stratifier (liaison/neuropsychiatry clinics), and trial arm. The model also contains participant-varying random intercepts to account for any over-dispersion. Potential clustering will be assessed in the model by considering including doctor-varying random intercepts to account for effects of the doctor delivering SMC, and therapist-varying intercepts in the CBT arm to account for therapist effects. Poisson model assumption checks are described below.
The model will be estimated using MI (specifically ICE) and will allow for missing outcome data under the missing at random (MAR) assumption. The analysis is valid provided this assumption holds; here this means that the observed variables driving missingness have been included in the ICE step.

Predictors of missingness, i.e. baseline characteristics and compliance with treatment in the CBT arm, will be included in the ICE step; this is aimed at ensuring that our MAR assumption is realistic.

In addition, all of the explanatory variables used in the analysis model will be included in the ICE step to ensure that the imputation model is at least as general as the analysis model. Importantly, the ICE step will also contain seizure frequency at 6 months and auxiliary variables for seizure outcomes to make a more realistic MAR assumption and gain precision.

The effect of departures from this MAR assumption on results will be assessed using sensitivity analyses[22].

**Analysis of secondary outcomes**

Secondary patient outcomes relating to DS severity and disability, health-related quality of life, well-being, global clinical improvement and satisfaction with treatment will be analysed using similar GLMMs. For example, continuous variables such as quality of life will be modelled using regression with random effects accounting for doctor or therapist clustering if necessary. Transformations will be investigated for secondary outcomes that are unlikely to be normally distributed. Binary variables such as seizure freedom in last 3 months (yes/no) will be analysed using logistic regression with random effects.

Similarly to the primary outcome analysis, secondary outcome measures at 6 months post randomisation will be used as auxiliary variables in the imputation model to account for missingness.
Secondary outcomes relating to the economic objectives are explained below in the health economic plan.

Statistical considerations

Missing items in scales and subscales

The number (%) with complete data will be reported. The ideal approach would be to use missing value guidance provided for scales. Where this is not available, scales will be pro-rated for an individual if 20% or fewer items are missing. For example, in a scale with 10 items, prorating will be applied to individuals with 1 or 2 items missing. The average value for the 8 or 9 complete items will be calculated for that individual and used to replace the missing values. The scale score will be calculated based on the complete values and these replacements.

Missing baseline data

We do not anticipate missing values in pre-randomisation variables. However, if we encounter missing baseline values then we can also use the MI process as explained above, or they can be singly imputed according to White and Thompson[23].

Method for handling multiple comparisons

There is only a single primary outcome and no formal adjustment of p-values for multiple testing will be applied. However, care should be given when interpreting the numerous secondary outcomes.

Method for handling non-compliance

In addition to the primary intention-to-treat analysis the effect of actually receiving treatment as defined in the protocol will also be estimated.
If non-compliance with treatment is high in the CBT arm, a complier-average causal effect (CACE) analysis will be considered. CACE analysis examines the effect of CBT among compliers. Complier status is only observable in the CBT arm. Instrumental variables methods using randomisation as an instrument for CBT receipt will enable estimation of CACE without incurring bias[24].

Model assumption checks
In order to assess the adequacy of the Poisson regression model for the primary outcome, we will first look at the basic descriptive statistics for the count data. A Poisson model assumes that each seizure is independent of each other, and the count mean and variance are similar; therefore if they are very different, this may be an issue of over-dispersion. A goodness-of-fit chi-squared test will assess the model fit; if the test is not statistically significant then the Poisson model fits well and distributional assumptions are met. However, if the Poisson assumptions are violated then a negative binomial model may be considered more appropriate because an extra parameter can model the over-dispersion.

For the secondary outcomes regression residuals will be plotted to check for normality and outliers.

Subgroup analyses
No subgroup analyses are planned. The study is not powered to investigate interaction effects. In addition, this analysis plan does not cover any further secondary analyses of the trial dataset. Mediator and exploratory moderator analyses may be performed after the primary trial data analysis.

Software

Data management
An online data collection system for clinical trials (MACRO; InferMed Ltd, London, UK) will be used. This is hosted on a dedicated server at King’s College London and managed by the KCTU.

Statistical analysis
Stata version 14.0 (StataCorp, College Station, Texas) will be used for data description and inferential analysis.

Economic analysis plan
Health economic objective and measures
We will take both a health/social care and a societal perspective in the assessment of cost-effectiveness. Societal costs include lost employment and care from family/friends. Permission to use Hospital Episode Statistics (HES) data will be applied for in order to measure inpatient and other hospital use; however, if this is not possible then service use will still be measured with the Client Service Receipt Inventory[25] questionnaire which is collected at baseline, and at 6- and 12-month follow-ups, and this will supplement information on number of therapy sessions provided.

Costs will be calculated by combining the service use data with recognised unit costs [26, 27]. Wage rates will be used to value lost work and care from family/friends. Intervention unit costs will be based on salaries, overheads, training and supervision.

Costs will be compared between the two arms at 6- and 12-month follow-up (the latter being the cumulative costs over the entire follow-up period). Baseline costs will be controlled for in a bootstrapped regression model (given the likely skewed data distribution). We will report 95% percentile confidence intervals around the cost difference at each time point.
To assess cost-effectiveness, costs will be combined with change in DS frequency and also quality-adjusted life-years (QALYs) derived from the EQ-5D-5L[28] using the area-under-the-curve approach. Incremental costs and outcomes will be obtained via regression models and 1000 differences obtained from bootstrapped resamples will be plotted on a cost-effectiveness plane to investigate uncertainty around the incremental cost-effectiveness ratio obtained from point estimates.

Sensitivity analyses will be conducted with missing follow-up costs and QALYs derived via multiple imputation. If an individual has a missing number of service contacts or a missing EQ-5D domain score then the median of others with these data will be used.

Other sensitivity analyses will use QALYs derived via the SF-6D from the SF-12v2[29,30]. Furthermore, we will use homecare workers as alternative values for informal care.

There has been limited previous research in this area and this trial will provide evidence on the impact of CBT in DS patients over a one-year follow-up.

**Trial status**

The CODES Trial started recruitment into phase I in October 2014 and randomised its first participant into phase II in January 2015; recruitment is currently ongoing.

**List of abbreviations**

AE: Adverse event; AR: Adverse reaction; CACE: Complier average causal effect; CBT: Cognitive Behavioural Therapy; CODES: Cognitive behavioural therapy versus standardised medical care for adults with dissociative non-epileptic seizures; DS: Dissociative seizures; EEG: Electroencephalograhic; EQ-5D-5L: 5-level European Quality of Life-5 Dimensions; GLMM: Generalised linear mixed models; ICE: Imputation by chained equations; IoPPN: Institute of
Declarations

Ethics approval and consent to participate

Ethical approval was given centrally for all of the study centres by National Research Ethics Service Committee London – Camberwell St Giles, reference number 13/LO/1595. Informed consent will be obtained from all participants in the study prior to randomisation.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

AC has been the unpaid President of British Neuropsychiatry Association, is a paid editor of the Journal of Neurology, Neurosurgery and Psychiatry, and has received fees for expert testimony in court on a range of neuropsychiatric topics including dissociative seizures. TC is a paid editor of the Journal of Mental Health. MR receives payments from Elsevier in his role as Editor-in-Chief of Seizure–European Journal of Epilepsy. JS runs a free website for patients with functional and
dissociative neurological symptoms including DS (www.neurosymptoms.org) that is mentioned in study materials. None of the other authors have any competing interests to declare.

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**Authors’ contributions**

EJR drafted and finalised the background, trial design, data analysis and inferential analysis sections. LG (chief investigator) participated in the trial design section and helped to draft the manuscript. PM wrote the health economics analysis plan. IP provided details of constructing the outcome measures. TC provided comments on the trial design section. JDCM, MPR and JM contributed to the trial design and implementation. MR provided suggestions on the background and trial design sections. NM contributed to the trial design and implementation. JS provided suggestions on the background and trial design sections. AC provided suggestions on the trial design section. SL provided support in
writing the trial design and analysis sections and helped to draft the manuscript. All authors read
and approved the final manuscript.

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Figure 1: CODES CONSORT diagram