NORWICH CTU

ICALM (Interpersonal Counselling for Adolescent Low Mood)

Interpersonal Counselling for Adolescent Depression delivered by Youth Mental Health Workers without Core Professional Training: A Feasibility Randomised Controlled Trial

Statistical Analysis Plan (SAP)

Version 0.2

19th August 2022

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SAP REVISION HISTORY

Document Name	Version No.	Reason for Revision	Effective Date
ICALM SAP	V0.1	Comments from oversight committee	19-08-2022

PURPOSE:

The purpose of this document is to provide a template for the writing of the SAP. This template is consistent with the guidance provided by Gamble et al., *Guidelines for the Content of Statistical Analysis Plans in Clinical Trials*, JAMA;2017:318;2337-2343

RESPONSIBILITY:

The Trial Statistician is responsible for the writing and maintenance of the SAP but may delegate these to another statistician in the trial team. The plan should be written in collaboration with the Chief Investigator and Trial Manager both of whom should approve the plan.

1.0 Administrative Information

Sponsor :	Norfolk and Suffolk NHS Foundation Trust
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Chief Investigator :	Jon WILSON
Trial Statistician :	Lee SHEPSTONE
UKCRC Trials Unit :	Norwich CTU
Latest Protocol :	Version 1.9 (12th July 2021)

2.0 Introduction

2.1 Background and Rationale

There is extensive and growing demand for services to meet the needs of young people with poor mental health (1). Depression is a common health problem during adolescence. Adolescent lifetime prevalence of major depressive disorder (MDD) is 11-20% (2,3). However, mild/sub-threshold depression is much more common in adolescents than full MDD (4). Such mild depression is associated with significant personal and public health consequences (5) and is a strong predictor for future onset of full MDD (6). Depression in adolescence predicts a range of adverse outcomes in adulthood, including ongoing mental health problems (7), poorer physical health (8), and social, legal and financial problems (9), and is the most prevalent psychiatric disorder in young people who die by suicide (10). The total annual cost of depression in England has been estimated to be at least £20.2 billion (11). However, there is evidence that prompt psychological intervention can prevent relapse and recurrence (12) and therefore intervening early, before depression symptoms become severe, could generate substantial savings.

The majority of adolescents seeking treatment for depression have mild disorder (13). In the UK, such cases of mild depression are not likely to meet treatment thresholds for specialist (tier 3) child and adolescent mental health services (CAMHS). Instead, young people with mild depression are seen by staff working in local authority child and family services or tier 2 NHS-funded mental health services often delivered by third sector/voluntary agencies. Most of those working with depressed young people within these non-specialist services are not qualified mental health professionals and have no formal training in delivering evidence-based treatments for people with depression.

Current guidelines for the treatment of mild depression in children and young people (14) recommend simple non-specific psychosocial strategies, such as non-directive supportive therapy. A recent large network meta-analysis has shown that while non-directive supportive therapy is better than a waiting list (i.e. no treatment) for adolescent depression, it is not significantly better than placebo (15). It is important to note that the primary studies included in this meta-analysis took place in a range of services for a range of severities of depression. No randomised controlled trials have taken place in the services described above, where most cases of mild depression are treated in the UK. Thus there is a clear lack of evidence as to how to treat young people in these services (16–18).

Interpersonal psychotherapy (IPT) is a NICE-recommended first-line treatment for adolescents with moderate to severe depression. IPT helps patients to understand the two-way links between their depressive symptoms and current interpersonal relationships. It also helps patients to improve their interpersonal relationships. In doing so, it aims to reduce depressive symptoms. Whereas non-directive supportive therapy aims '*to help patients accommodate to existing reality rather than try to help them change it*' (19), IPT focuses on helping patients to take active steps to improve their relationships in order to decrease their depressive symptoms. Theoretical influences on IPT included Adolf Meyer's 'psychobiological' approach, which emphasized patients' current interpersonal and psychosocial experiences (20); and Harry Stack Sullivan's 'interpersonal' approach, which conceptualized psychiatry as the scientific study of people and interpersonal processes (21). Both approaches contrasted with the

dominant psychoanalytic approach at that time, which emphasised intrapsychic processes over interpersonal relationships.

Meta-analyses have demonstrated IPT to be superior to control treatments for depression in both adults (22) and adolescents (15); and to lead to similar outcomes as cognitive-behaviour therapy in both age groups. Crucially, IPT has been shown to be significantly more effective than supportive counselling for depressed adolescents (23). Given the importance of interpersonal relationships in the causation of adolescent depression (16), and the developmental priority given to interpersonal relationships during adolescence, this approach has high face validity for this age group.

However, in common with other evidence-based treatments for adolescent depression, IPT must be delivered by a qualified mental health professional with extensive auth. As such, it is unlikely to be a feasible treatment option outside of specialist CAMHS. Interpersonal counselling (IPC) is an adaptation of IPT with three main differences: the treatment duration is shorter (3-6 sessions); it is designed for clients with mild depression; and it can be delivered by non-mental health professionals after participation in a brief (two day) training course.

IPC has been found to be an effective treatment for adults with mild to moderate depression (24,25). An adapted form of IPC designed to meet the needs of young people (IPC-A) has recently been developed and piloted by members of the research team of this proposal (PW and VC), but its effectiveness as a treatment for adolescent depression has yet to be tested. Although there are many similarities between adult and adolescent depression, there are also important differences, particularly in treatment response (16). Adult and young people's services also differ in their organisation, ethos and staff training (26). Therefore, it cannot be assumed that an effective treatment for adult depression can be transferred to adolescents without evaluation.

This study is intended to provide the information needed to progress to a full-scale clinical trial of IPC-A delivered by staff without core professional training (referred to in this application as 'youth mental health workers'). The training (including subsequent supervised casework) required to deliver IPC-A can be completed by staff without prior mental health qualifications in less than 12 weeks. Therefore, if found to be an effective treatment, training existing workers as IPC-A therapists could facilitate a rapid and relatively low-cost expansion of the therapy workforce in line with NHS England and government commitments.

2.2 Objectives

Research question: Is a full-scale RCT of interpersonal counselling for young people with mild depression delivered in non-specialist community services feasible?

The proposed research is designed to inform a future trial of the effectiveness and cost-effectiveness of the intervention (interpersonal counselling for adolescents with mild depression). The aim of the proposed research is to answer the following feasibility questions which arise from the variability in service models across providers of non-specialist mental health support for young people:

- Are trial procedures, including recruitment (of participants and therapists), randomisation, research assessments and follow-up, feasible and acceptable?
- How are IPC-A and treatment as usual (TAU) delivered and how and why does intervention delivery vary across differing service contexts?
- To what extent does contamination of the control arm occur and should it be mitigated against in a future trial?
- Does the interval estimate of benefit of IPC over TAU in depression scores at post-treatment include a clinically significant effect?

3.0 Study Methods

3.1 Trial Design

ICALM is an individually randomized feasibility clinical trial. It is a parallel design with two arms, IPC-A or TAU, participants allocated equally to each arm.

3.2 Allocation

Randomisation of participants is coordinated remotely by the Norwich Clinical Trials Unit (CTU). Participants are randomised in a 1:1 allocation ratio, using a stochastic minimization algorithm to minimise imbalance between groups in baseline symptom severity, gender and study site. Allocation is managed by the Data Management Team at Norwich CTU via a web-based system; it is not accessible by anyone outside of this team, including the research team, trial therapists and participants in order to maintain allocation concealment.

3.3 Sample Size

The target sample size was 60 eligible participants randomised into the study. This sample size is not based upon estimation of efficacy but is in keeping with published suggestions (e.g. 32) and believed to be practically possible within the limits of the project. Further, it should enable rates of recruitment and retention to a reasonable degree of precision. Assuming an attrition rate of around 20%, a sample of 60 would provide a 95% confidence interval of width 20% (i.e. +/- 10%). For a recruitment rate of around 50% the interval width would be around 25% (i.e. +/- 12.5%).

3.4 Framework
ICALM is a feasibility randomized controlled trial to inform a future, large scale, trial. It is not designed to test treatment efficacy to any specific degree of precision. A frequentist framework is used for analysis.

3.5 Timing of outcome assessments
Assessment visits are timed for 5 weeks, 10 weeks and 23 weeks post-randomisation.

3.6 Interim analyses and stopping guidance
No formal stopping rules exist. The DMC may wish to consider formal interim analyses at the request of the sponsor, funder or TSC.

3.7 Timing of analyses
The final analysis of feasibility and efficacy outcomes will occur once all data have been collected, the database locked and the statistical analysis plan (this document) agreed.

4.0 Statistical Principles

4.1 Levels of statistical significance
Statistical significance will be at the conventional two-tailed 5% level with associated 95% confidence intervals. No adjustments for multiple hypothesis testing will be made.

4.2 Treatment adherence
There is no defined level of treatment considered adherent for statistical analysis purposes. One objective of the study is to consider treatment levels as part of the feasibility assessment. Attendance or non-attendance at planned therapy sessions, and location of sessions will be collected by therapists in both treatment arms

4.3 Protocol deviations
Protocol deviations are recorded. Any that may be relevant to the analysis will be discussed with the trial statistician.

4.4 Analysis populations
The efficacy analysis will be with respect to the Intention-to-Treat principle. Subjects with available data will be analysed according to the treatment to which they were allocated irrespective of actual treatment received.

5.0 Trial Population

5.1 Screening data
The age and gender of those screened for study have been collected and will be reported for purposes of comparison between those participating and those ineligible or non-consenting.

5.2 Eligibility
Participants are young people, 12 to 18 years of age, accessing participating services via the service's

standard referral pathways. Young people are triaged and assessed according to each service's standard procedures. If this assessment identifies low mood as a presenting difficulty, the case is discussed with a clinical member of the research team to ascertain likely suitability for the trial. The service will have the option of using the RCADS depression scale to help determine suitability, with a cut-off of 11 or over suggesting suitability (this cut-off is not an absolute).

Potentially suitable young people are invited to participate and those who express an interest meet with the trial's research practitioner who will carry out informed consent procedures and screen the young person to ensure they meet entry criteria.

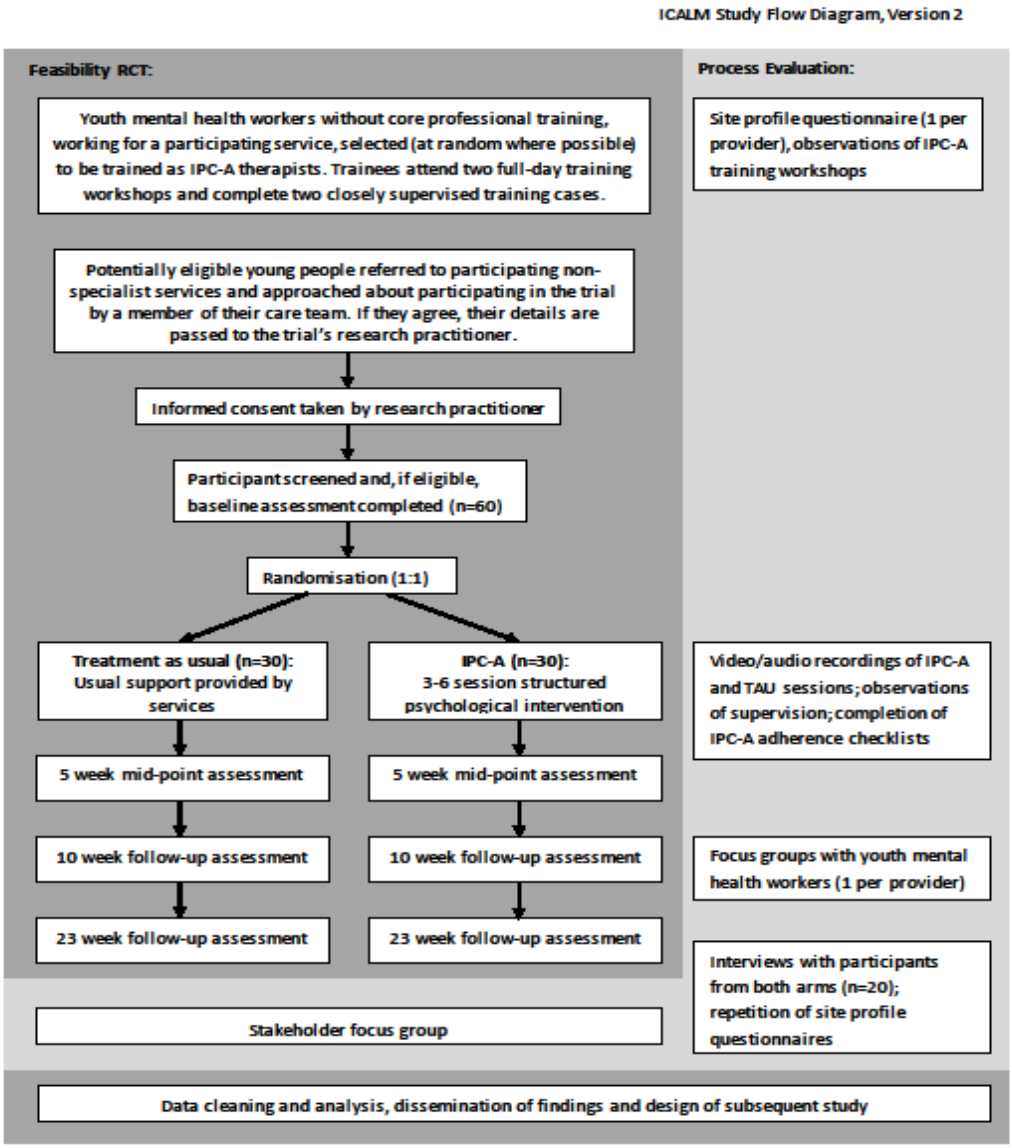
5.2.1 Participant Inclusion Criteria

- Aged 12-18 years
- Seeking help for low mood (as the primary presenting difficulty)
- Able to provide written informed consent or, for under 16s, written informed assent and parent/guardian consent
- Of a level of illness where they would normally receive treatment from the service

5.2.2 Participant Exclusion Criteria

- Learning disability necessitating non-mainstream schooling
- Current psychotic disorder
- Current substance dependence
- Current significant suicidal ideation (K-SADS-PL – 'suicidal ideation' threshold – 'often thinks of suicide and has thought of a specific method')

5.3 Recruitment and participant flow



5.4 Withdrawal information

Participants' continued willingness to participate is confirmed at each study contact before commencing any research procedures. Participants are free to withdraw from the study at any time up until the time of data analysis. Data collected up to the point of withdrawal will be used if the participant (and their parent/carer in the case of participants under 16) consents to this. Reasons for withdrawal will be summarized and presented within the CONSORT flow-diagram and elsewhere in report text as necessary. These may be grouped together under common reasons. These maybe relevant to the design of a future, full-scale trial.

5.5 Baseline participant characteristics

The following participant data is collected at baseline (face-face, telephone and/or video call interview, +/- internet delivered questionnaires):

- Demographic characteristics of young person
- Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), depression section (27,28)
- Revised Children's Anxiety and Depression Scale (29)
- Family Assessment Device (30)
- Cambridge Friendships Questionnaire (31)
- Employment, Education or Training in previous 4 weeks (NEET status)
- Short Warwick-Edinburgh Mental Wellbeing Scale (32)
- Modified Client Service Receipt Inventory (33)
- Child Health Utility 9D (34)

These will be summarized and tabulated by arm.

6.0 Analysis

6.1 Outcome definitions

The primary output of the research will be the design of a subsequent full-scale trial. The data from this feasibility stage will be assessed against the following criteria and recommendations regarding the suitability of the proposed design for the full-scale trial will be made.

a) Recruitment rate is at least 80% of target, i.e. at least 48 individuals randomized.

b) At least 70% of those randomised to receive the intervention attend at least three therapy sessions within the 10 week treatment window.

c) Follow-up assessments are completed by at least 80% of participants at 10 weeks and 70% of participants at 23 weeks.

d) At least 80% of IPC treatment sessions reviewed meet treatment fidelity criteria.

e) Contamination of the control arm can be sufficiently limited for individual randomisation to be justified

f) The mean RCADS depression scores of the IPC-A and TAU groups at 10 weeks are indicative of a clinically significant difference in depression (3 points), i.e. a 3 point benefit is included within the 95% confidence interval.

6.1.1 Primary Efficacy Outcome

The primary efficacy outcome is the depression score of the Revised Children's Anxiety and Depression Scale (RCADS) at 10 weeks.

6.1.2 Secondary Efficacy Outcomes

At the 5 week visit:

- Revised Children's Anxiety and Depression Scale (29)
- Family Assessment Device (30)
- Cambridge Friendships Questionnaire (31)

At the 10 and 23 weeks visits:

- Revised Children's Anxiety and Depression Scale (29)
- Family Assessment Device (30)
- Cambridge Friendships Questionnaire (31)
- Employment, Education or Training in previous 4 weeks (NEET status)
- Short Warwick-Edinburgh Mental Wellbeing Scale (32)
- Modified Client Service Receipt Inventory (33)
- Child Health Utility 9D (34)

6.2 Analysis Methods

Recruitment and retention rates will be estimated with 95% confidence intervals (CIs). Assuming sufficient information, time until drop-out will be analyzed using 'time-to-event' methods, i.e. in an effort to identify baseline factors likely to be related to drop-out.

The primary outcome measure is the RCADS depression score at 10 weeks. Although the current study is not designed to assess efficacy, the mean between-group difference will be estimated using a general linear model including baseline RCADS depression score as a fixed covariate. Ideally, the treating therapist would be included as a random effect within a multi-level model (therapists being nested within treatment arm). However, due to a paucity of data (only two therapists and three participants in the intervention arm) this will be omitted. A 95% CI will be constructed to assess whether the treatment benefit is feasibly greater than the minimal clinically significant difference, i.e. whether or not it is included within the CI. A similar approach will be undertaken for the secondary outcome measures. Secondary outcomes will be presented descriptively by treatment arm.

The rate of completion of each outcome measure will be reported. If appropriate, depending on the proportion of missing values, multiple imputation will be undertaken and between-group differences re-estimated for the primary outcome as a sensitivity analysis. Further parameters, such as within group variation, needed for the design of a subsequent full-scale trial, will also be estimated.

6.3 Missing Data

The amount of missing data for all efficacy outcomes will be presented in reports. This will inform the design of a future study. If the level of missing data for the primary outcome is between 50% and 95%, a sensitivity analysis will be carried out using Multiple Imputation. Twenty data sets will be imputed and Rubin's rules used to estimated standard errors. There are no plans to impute missing data for any further data.

6.4 Additional analyses

No further sensitivity or subgroup analyses are currently planned.

6.5 Safety analyses

Frequencies of adverse events, by treatment arm, will be reported. Details of serious adverse events, including relatedness, by treatment arm, will also be reported, according to definitions provided in Section 11 of the protocol.

6.5 Software

Statistical analyses will be conducted using SAS v9.4.

7.0 References

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