RISA-IPD

*Reduc**I**ng **S**elf-harm in **A**dolescents: **I**ndividual **P**atient **D**ata meta-analysis*

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Protocol Version 2.1 27 September 2019
UoL Grant Number: RG.PSRY.116370
HTA Reference Number: 17/117/11
Prospero Registration: TBC
University of Leeds Ethics: MREC 18-098

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Contents

1 Summary of Research

1.1 Background

Self-harm is common in adolescents and a major issue of public health concern in the UK and globally[1]. Evidence suggests that up to 10% of young people report self-harm in the previous year, and suicide is the second commonest cause of death in 10-24 year olds[2]. Self-harm in adolescents has serious consequences, with rates of death from any cause showing a four-fold and suicide a ten-fold excess risk[3]. Non-fatal repetition is common with one-year rates of hospital re-attendance at 18%[4].

Any intervention that reduced self-harm would, as well as saving lives, result in significant reductions in family and peer distress. Effective interventions would also reduce significantly the cost to the health service in providing support for repeated self-harm. However, a single effective intervention to prevent repeat self-harm has not yet been identified[5,6]. Published studies to date have often been small with mixed and varied samples. Those who self-harm, do so for a variety of different reasons. It is therefore possible that there are sub-groups of adolescents for whom certain treatments may be effective.

An individual patient data (IPD) meta-analysis would provide more reliable estimates of the effects of therapeutic interventions for self-harm than conventional meta-analyses that rely on aggregated information and reported analyses[7], and would permit meaningful subgroup analyses previously unavailable to individual studies due to the increased sample size.

1.2 Aims

To conduct an individual patient data meta-analysis (and meta-regression) of existing randomised controlled trials of therapeutic interventions to reduce subsequent self-harm in adolescents in order to identify subgroups of adolescents in whom a therapeutic intervention for self-harm shows some evidence of benefit (or dis-benefit).

1.3 Plan of Investigation

To perform an updated and refined systematic literature search to select published and unpublished randomised controlled trials of therapeutic interventions to reduce subsequent self-harm in adolescents who have already self-harmed and presented to services.

Authors of identified eligible studies will be contacted and invited to share individual-participant-data (IPD) and collaborate with us. IPD will be securely transferred to the statisticians in Leeds. Where IPD is not available, we will use (published) aggregated data. After data cleaning and manipulation, we will conduct a meta-analysis and meta-regression of data from each trial.

1.4 Potential Impact

If the meta-analysis indicates clearly that certain sub-groups of young people do better (or worse) with certain types of intervention, we would expect significant changes in the way that services are delivered to those groups of young people. If the evidence is less clear-cut it is possible that avenues of future research are suggested using more tailored interventions for sub-groups of young people, leading to new and better targeted randomised controlled trials to confirm (or refute) the hypotheses raised by our results.

2 Plain English Summary

Self-harm is common in teenagers. In surveys, 10% report self-harm in the past year. Teenagers who self-harm are at risk of repeating self-harm. Suicide is the second commonest cause of death in 10 to 24-year olds, after road traffic accidents. Teenagers who self-harm do so for a variety of personal, family and social reasons. Those who have self-harmed are likely to experience more emotional difficulties and difficulties relating to people later in life. Their families and those close to them report experiencing considerable distress.

If we had effective treatments to reduce the likelihood of repeat self-harm we could save lives, reduce distress and improve life chances. Unfortunately, despite a number of different research projects, we still have no clear evidence of an effective treatment intervention that will reduce the likelihood of further self-harm if someone has already self-harmed. Much of this existing research has involved relatively small samples. In addition, it has included groups of young people who have self-harmed in different ways and for different reasons.

It is possible that the treatments tried so far have not been shown to be effective because those treatments are helpful for some young people who have self-harmed and not others and these benefits have been hidden in the overall result.

To address this possibility, we will gather information from research that has already taken place, combine this information and conduct further analysis. We will focus on a type of research known as a Randomised Controlled Trial (RCT). This is a research study that randomly puts participants into two or more different groups. The participants in each group are given a different treatment and the results of the treatments are analysed to see which is more effective. By combining information from these types of study we will have data on a large group of young people who have received a range of different interventions. Dividing this large group into smaller groups (for example, boys vs girls, those with depression vs those without, those using different methods of self-harm, those receiving individual treatments vs other types of treatment etc.) may help identify 'sub-groups' of young people who have self-harmed that do better (or worse) than others on particular treatments.

This might enable us to make recommendations, 1) to clinicians to guide the sort of treatment to offer to particular groups, and 2) to researchers about targeted treatments that could be further evaluated for specific sub-groups.

The research team is well placed to conduct this research. We have conducted many of the randomised, controlled trials of interventions in self-harm in the UK and therefore already have access to and an understanding of the data. We have also published research on the treatment of self-harm in adolescents that involves finding all the relevant studies by searching databases of all published studies and then combining their results. Between us we have clinical child mental health expertise and statistical expertise in analysing large and complex data sets. We will also work with an expert Patient and Public Involvement group of young people, set up specifically to support this study, to ensure that we take into account the views of service users in designing, conducting and sharing the results of the research.

3 Background and Rationale

3.1 What is the problem being addressed?

Self-harm in adolescents is a global public health problem, with 10% of adolescents self-

reporting self-harm within the last year[8] and suicide the second highest cause of death in 10 to 24-year olds, after road traffic accidents[9].

Preventing suicide is the focus of a major cross-government strategy to save lives (Preventing Suicide in England, Department of Health, 2012[1]), with regular updates published on progress to meet the strategy targets[10]. This project relates directly to three of the strategy's key objectives: 1, Reduce the risk of suicide in key high-risk groups; 2, Tailor approaches to improve mental health in specific groups; and 6, Support research, data collection and monitoring.

Self-harm can take a variety of forms. In this project, we will align with common UK and European practice and define self-harm as any form of intentional non-fatal self-poisoning or self-injury (including cutting, taking excess medication, attempted hanging, self-strangulation, jumping from height, running into traffic), regardless of suicidal intent. This includes definitions of non-suicidal self-injury (NSSI) commonly used by US researchers and suicidal behaviour where lack of intent is assumed by reference to the method of self-harm. We believe there is sufficient evidence that this distinction is unhelpful in many cases[3,11]. Self-harm is thus a behaviour not a diagnosis. Adolescents who self-harm do so for a variety of reasons and may have experienced a wide range of potential predisposing, precipitating and perpetuating factors[12,13]. This approach is adopted by the National Institute for Health and Care Excellence (NICE).

3.2 Why is this research important in terms of improving the health and/or wellbeing of the public and/or to patients and health and care services?

Self-harm is common. An international, anonymous, survey administered to 30,477 14 to 17 year olds in six European countries (including England) and Australia found 13.5% of girls (4.3% boys) reported self-harm in their lifetime, with 8.9% prevalence in the past year (2.6% boys)[14]. Prevalence rates may be increasing; records from 674 GP practices in the UK for those aged 10 and 19 between 2001 and 2014 showed incidence rates for most age and gender ranges remaining stable but a sharp increase of 68% in females aged between 13 and 16 years old, rising from 45.9 per 10,000 in 2011 to 77 per 10,000 in 2014[15]. Self-harm in adolescents has serious consequences, with rates of death from any cause showing a four-fold and suicide a ten-fold excess risk[3], resulting in potentially avoidable burdens of life-years lost and family and peer distress. Non-fatal repetition is common with one-year rates of hospital re-attendance at 18%[4], and repetition over 8 years 27%[16]. In an Australian cohort study, the self-harm group was more likely to experience a range of difficulties in their adolescent years including mental health problems and tobacco, alcohol and illicit substance use. Later in life, this cohort was also more likely to experience financial hardship, divorce or separation, and other social disadvantages[17]. Any intervention that reduced self-harm would, as well as saving lives, result in significant reductions in family and peer distress. Effective interventions would also reduce significantly the cost to the health service in providing support for repeated self-harm.

3.3 Evidence explaining why this research is needed now

A single effective intervention to prevent repeat self-harm has not yet been identified[5]. A recent systematic review (19 RCTs, n=2176) found a small overall effect on repetition, with suggestive effect sizes for three specific interventions[6]. Studies with strong family involvement and substantial treatment dose have shown significant reductions in self-harm[6]. A recent large, retrospective, registry-based matched cohort study (N=5,678) has shown lower long-term risk of self-harm in those receiving psychosocial treatments compared with those who do not, but numbers needed to treat were large[18].

The largest RCT of a psychological intervention following self-harm (n=832)[19], showed no overall benefit of family therapy but did identify moderators related to ease with which the young person and their family could talk about feelings, that either made family therapy more or less likely to be effective compared with treatment as usual.

Most published studies have been pragmatic and have recruited participants presenting to services without major restrictions. Samples have often been small and heterogeneous. It is therefore possible that in the total population of adolescents who self-harm there are subgroups who respond better to all or some interventions. We also know that factors such as age, gender, LGBT status, number of previous self-harm attempts, method of self-harm, psychiatric history and status (in particular depression[20]) carry increased risk for later repetition and sometimes for completed suicide. The recent National Confidential Inquiry into Suicide and Homicide indicated that out of 285 suicide deaths that occurred in 74 youths aged 10-20, 52% had a history of self-harm, while 58% expressed thoughts of suicide or hopelessness[21]. This raises the possibility that either treatment and/or adolescent and family variables may predict better (or worse outcomes) and be important mechanisms underpinning the effectiveness of interventions.

IPD meta-analysis provides more reliable estimates of the effects of therapeutic interventions for self-harm than existing conventional meta-analyses that rely solely on aggregated information and reported analyses[7]. It also permits meaningful subgroup analyses previously unavailable to individual studies due to the increased sample size. It allows appropriate handling of randomisation and treatment-related clustering, repeated measures, missing data, non-adherence, consistent adjustment for baseline covariates. This meta-analysis represents the best way of exploring these possibilities and holds out the prospect of being able to make recommendations for researchers on what treatments might be indicated (or perhaps contraindicated) for the adolescent who self-harms presenting to UK clinics.

4 Aims and objectives

We aim to build on previous systematic reviews including our own[5,6,22-24], our knowledge of the self-harm literature, relevant methodological developments and contacts with the self-harm research community to conduct an IPD meta-analysis (and meta-regression) of randomised controlled trials of any therapeutic intervention (compared with any comparator) to reduce subsequent self-harm in adolescents (aged 11-18) who have already self-harmed and presented to services.

The ***R**educ**I**ng **S**elf-**H**arm in **A**dolescents: **I**ndividual **P**atient **D**ata meta-analysis **(RISA-IPD)*** project aims to identify subgroups of adolescents in whom a therapeutic intervention for self-harm shows some evidence of benefit in order to guide future primary research. The project objectives are to:

1. Conduct a systematic literature search and systematic study selection to identify relevant research teams and studies;

2. Invite identified research teams to contribute data to enable us to form a collaborative group and conduct an IPD meta-analysis;

3. Conduct an IPD meta-analysis with the following objectives:

i. Provide updated estimates of the pooled treatment effect of any therapeutic intervention for self-harm compared to any non-active control;
ii. Identify subgroups of adolescents in whom any therapeutic intervention is effective
iii. Provide estimates of the pooled treatment effects of specific types of therapeutic intervention compared to any non-active control for self-harm in adolescents;
iv. Identify subgroups of adolescents for whom specific types of therapeutic interventions for self-harm are effective;

4. Provide clearly defined research recommendations for future clinical practice and RCTs.

5 Research Plan / Methods

We will conduct an updated systematic literature search and systematic study selection of published randomised controlled trials of therapeutic interventions to reduce subsequent self-harm in adolescents who have already self-harmed and presented to services. We will obtain IPD from identified studies and form a collaborative group consisting of RISA-IPD researchers and investigators from identified studies in order to conduct an IPD meta-analysis and meta-regression of individual-level data from each trial following the guidelines of the Cochrane group for IPD meta-analyses (http://methods.cochrane.org/ipdma/). We will summarise the evidence by synthesising the data whilst preserving the randomisation and clustering of data within studies. The 'PICO' structured question addressed in our project is summarised below.

Population	Adolescents aged 11-18 who have self-harmed at least once and consequently presented to clinical services
Intervention	Any type of intervention one of the aims of which is to reduce subsequent self-harm
Comparator	Any inactive treatment (e.g. treatment as usual, management as usual, placebo or attention-control) or active control
Outcomes	Repetition of self-harm.

5.1 Health technologies being assessed:

Any type of intervention the aim of which is to reduce subsequent self-harm. This includes psychological or pharmacological interventions, with/without individual, group or family involvement; delivery of social/service support; and interventions of any intensity (number/length of sessions). Prevention based interventions not targeted specifically at adolescents who have presented to clinical services with self-harm are excluded.

5.2 Search Strategy

A scoping search in 2018 identified systematic reviews that identified RCTs for our meta-analyses; see Appendix 6 for details of 22 studies identified from our scoping review meeting RISA-IPD eligibility criteria. However, 'gaps' were found in their search strategies and inclusion criteria indicating eligible trials may have been missed if they are unpublished, recently published =or have <85% adolescents as participants.

Our search strategy seeks all eligible RCTs by four routes:

i) From the scoping search, RCTs cited in 5 systematic reviews with similar inclusion criteria to our study[5,6,22-24];

ii) From the scoping search, RCTs cited in 2 adult self-harm systematic reviews[25,26], to identify RCTs with a small number of adolescents that may be excluded from the 5 adolescent reviews; and

iii) Literature search for systematic reviews of self-harm in adolescents, updated and across a wider set of databases then the scoping search – see Appendix 4 for search strategy.

iv) Literature searches for trials published since 2015, unpublished trials (no date restriction), and ongoing trials – see Appendix 5 for search strategy.

Trials with a low absolute number of adolescents (≥20) will be included only where the IPD can be extracted (aggregated data from RCTs with mixed age ranges will not be included if the IPD is not available). We will avoid outcome reporting bias by reviewing trial protocols to ensure awareness of studies where data were collected regardless of final reporting of results.

We will adhere to EUnetHTA search guidance[27]. The Information Specialist and core team will collaborate to develop a search strategy consisting of text words and subject headings for self-harm, suicide behaviours, adolescents, and RCTs. The Cochrane Collaboration RCT filter will be used to identify trials in Medline. Databases and information resources will include Medline 1946+ EMBASE 1947+, PsycINFO 1806+, Cochrane Library, Epistemonikos, ProQuest Dissertations & Theses A & I 1743+, PROSPERO, Web of Science Core Collection 1900+, ClinicalTrials.gov, ICTRP trials search portal and the National Youth Mental Health Foundation database. Scoping searches indicated approximately 150 randomised controlled trials will be identified in 7 reviews and 1000 records will be identified by literature searches for trials. These results will be combined in an EndNote library and screened/selected using COVIDENCE software.

5.3 Review Strategy

Studies will be identified by an Information Specialist using the search strategy above, repeated nine months prior to the end of the project. Two reviewers (one Clinical, one Statistician) will review titles and abstracts to select trials using agreed eligibility criteria (see section 5.6), referring to full text and a third nominated reviewer as necessary. The reference lists of included trials will be checked for further relevant trials. We estimate approximately 25 RCTs will satisfy our inclusion criteria; see Appendix 6 for details of 22 eligible studies identified from our initial scoping review.

Papers, full protocols and statistical analysis plans will be obtained following enquiries to trial Chief Investigators and Statisticians, and data extracted on study quality by two reviewers (Clinical, Statistician); authors will be contacted for further information as required. We will use an extended version of the Cochrane Risk of Bias tool to assess study quality[28].

5.4 Design and theoretical/conceptual framework:

Design: IPD meta-analysis and meta-regression.

5.5 Inclusion/Exclusion Criteria:

5.5.1 SETTING/CONTEXT:

All countries of origin, any method of referral but ongoing intervention delivered in outpatient or community (school and voluntary sector) settings. This excludes intensive in-patient based interventions as these are unlikely to be applicable to UK settings.

5.5.2 STUDIES:

All randomised controlled trials, from the first available study, with any randomised design (e.g. individual or cluster), length of follow-up and quality, in which data relating to self-harm or suicide attempts have been collected.

We will include studies in which only a subset of participants meet our eligibility criteria where we are able to obtain IPD for eligible participants, i.e. studies with only a subset aged 11-18, or not all having self-harmed at least once prior to randomisation. Trials with less than 20 eligible participants will be excluded. This is to ensure the logistical effort in obtaining, cleaning, and organising the data is commensurate with the contribution of the dataset to the analysis.

Of necessity, studies will be excluded from the primary IPD analysis if it is not possible to reach agreement with study authors to share data, or not possible to obtain good quality translations of non-English reports within 2 months of the start of analysis (month 13). Sensitivity analysis (Section 5.7.5) will incorporate aggregate data from studies lacking IPD.

5.5.3 PARTICIPANTS:

All adolescents of any gender or ethnicity,

I. aged 11-18, where 18 is defined as up to the 19th birthday at the point of randomisation.
II. who have self-harmed at least once prior to randomisation and consequently presented to clinical services, where self-harm includes suicide attempt and excludes suicidal ideation without explicit self-harm.

No restrictions are placed on whether participants have comorbid mental or physical health conditions or intellectual disability.

5.5.4 INTERVENTIONS:

All randomised trial arms involving any type of intervention, delivered by any type of care provider(s), one of the aims of which was, to reduce subsequent self-harm. This includes psychological or pharmacological interventions, with/without individual, group or family involvement; delivery of social/service support; and interventions of any intensity (number/length of sessions) including self-help.

Excludes prevention based interventions not targeted specifically at adolescents who have presented to clinical services with self-harm, and intensive in-patient based interventions.

Controls: Any inactive (e.g. treatment as usual, management as usual, placebo or attention-control) or any active control.

5.5.5 OUTCOMES:

The primary outcome is repetition of self-harm from randomisation to last available follow-up over a maximum follow-up period of two years (and is thus binary). Self-harm is defined as any form of intentional non-fatal self-poisoning or self-injury (including cutting, taking excess medication, attempted hanging, self-strangulation, jumping from height, running into traffic), regardless of suicidal intent. This includes definitions of non-suicidal self-injury (NSSI) commonly used by US researchers and suicidal behaviour where lack of intent is assumed

by reference to the method of self-harm. Self-harm can be self-reported.

Secondary outcomes are: longitudinal, where possible, time to repetition of self-harm, general psychopathology, depression, suicidal ideation, QoL, death of adolescent.

5.5.6 JUSTIFICATION OF INCLUSION/ EXCLUSION CRITERIA:

The eligibility criteria are based on the HTA commissioning brief, clinical practice in the NHS and the need for our findings to be relevant to that practice.

An age range of 11-18 enables inclusion of the entire sample in the majority of good quality studies pre-identified and coincides with the end of schooling in the UK and the transition from Child and Adolescent to Adult Mental Health services is a logical age range for 'adolescents'.

The brief specified "Adolescents who have engaged in self-harm and presented to clinical services", we have therefore excluded studies where inclusion was based on suicidal ideation alone, or where there was no evidence of presentation to clinical services following self-harm. Suicidal ideation is common and not necessarily predictive of self-harm. Evidence suggests that interventions may bring about apparently positive changes in suicidal ideation but not have any impact on subsequent self-harm. For this reason, we have also chosen self-harm, not changes in suicidal ideation as our key outcome of interest. Where studies include a mixture of participants, some who have self-harmed as defined above and some with only suicidal ideation we will seek to include just those who have met our definition of self-harm.

We have chosen a broad definition of self-harm aligning our study with common UK and European practice and defining self-harm as any form of intentional non-fatal self-poisoning or self-injury (including cutting, taking excess medication, hanging, self-strangulation, jumping from height, running into traffic), regardless of suicidal intent. This definition includes definitions of non-suicidal self-injury (NSSI) commonly used by US researchers and suicidal behaviour where lack of intent is assumed by reference to the method of self-harm.

Generally, we have set our eligibility criteria for studies, treatment arms, care providers and participants independently of how easy it will be to include them. We will then deal with missing studies, arms, care providers and participants in the analysis. This is important if we are to make generalisations to the populations of studies, care providers and participants.

5.6 Data collection:

5.6.1 ASSESSMENT OF RISK OF BIAS OF INCLUDED STUDIES:

The quality of included studies (i.e. those contributing IPD and/or aggregate data) will be evaluated independently by two clinical and one statistical reviewer using criteria recommended by the Cochrane Collaboration[28]. These cover random sequence generation, allocation concealment, blinding of participants, outcome assessment and missing data. We will use an extended version of the Cochrane Risk of Bias tool to further evaluate additional sources of bias common to complex intervention trials (e.g. allocation of therapists to patients, therapist level missing data). Each domain will be judged as contributing to a low, high or unclear risk of bias. A work instruction will provide specific detailed instructions about how this will be done, refined on the basis of initial piloting.

Assessment will take place following identification of eligible studies based on published

papers and protocols irrespective of the availability of IPD. Further assessment will be conducted for included studies with IPD to allow data quality to be assessed in more detail. Studies will be included in the primary analysis regardless of study quality and adjusted for in planned meta-regression; sensitivity analyses will exclude studies judged as having a high risk of bias.

5.6.2 COLLABORATION WITH STUDY AUTHORS:

As recommended by MRC and the Cochrane Collaboration[29,30] we will invite one senior author of each eligible study to join a formal study collaborative group. The active collaboration of authors of primary studies will ensure that the data used are properly understood and used appropriately in the analysis. The multidisciplinary, cross-cultural membership of an IPD collaborative group will provide a more global and balanced interpretation of the meta-analysis results.

The Collaborative Group will have two formal meetings, the first relatively early in the project to review progress generally and specifically to discuss and review the analysis plan. The second meeting will take place towards the end of the project and will be to present the results of the meta-analysis and discuss their implications. Interpretation of results is likely to be influenced by nationality, culture, and clinical specialty as well as by patient characteristics, preferences, quality of life, and cost. For this second meeting, collaborative group members will be invited (fully-funded) to Leeds for a formal, face to face meeting. Regular, informal contact between the study team and collaborators is expected as questions arise about individual studies. We will invite members of the Collaborative Group to be involved in and comment on drafts of primary publications and to be named as authors of those publications.

5.6.3 ACCESS TO INDIVIDUAL PATIENT DATA (IPD):

A specific work instruction will provide details of this process. Following initial piloting of the process (using SHIFT as an example), we will contact study authors of eligible trials to seek the following IPD, in accordance with the study research objectives:

- Baseline patient demographic and clinical data: age, gender, ethnicity, intellectual disability, LGBT status, history of abuse, Looked After Children, self-harm method, number and timing of previous self-harm attempts, presence/severity of comorbid psychiatric (depression, borderline personality disorder and unemotional/ callous traits, eating disorders, anxiety disorders).
- Details of therapeutic intervention: attendance, session frequency and duration, intensity, overall duration, therapist details.
- Outcomes:
    - Repetition of self-harm, suicide attempt: incidence and time-to-event, and associated data (details of severity, method, outcome, type of event – self-reported or clinical/hospital presenting);
    - General psychopathology, Depression, Suicidal ideation and Quality of Life collected using standardised validated measures at baseline (pre-randomisation) and all available time-points post-randomisation
    - Death of adolescent: incidence and time-to-event

Collection and collation of data will be coordinated by the team based at the Clinical Trials Research Unit (CTRU) at the University of Leeds. Participating study authors will be asked to provide pseudonymised (without identifying data such as patient name or date of birth) datasets in whatever format is convenient to them (i.e. SAS, STATA, R, SPSS, Excel), along with data dictionaries, original statistical analysis plans and relevant statistical programming code where possible.

Data will be requested to be transferred via the Secure File Transfer service for the Clinical Trials Research Unit, which uses SSL encryption to transfer all messages and attachments, ensures messages and attachments stored on the service are encrypted using AES 256 encryption, and is FIPS 140-2 certified. Data received will be downloaded from the secure file transfer system and securely stored on CTRU systems with access only granted to the statistical team. Data will not be accessed by any third parties, nor will it be accessible across multiple organisations. CTRU has IG toolkit status (Code: ECC0010).

Formal data transfer agreements will be put in place between primary study leads for the data and the CTRU; CTRU Standard Operating Procedures and guidelines will be followed to protect the data.

We will make regular contact with study authors throughout the project and continue to seek to reach agreement with study authors to share data up to within 2 months of the end of analysis in order to allow sufficient resource for management of the data. IPD from studies will be excluded (by necessity) if it is not possible to reach agreement with study authors to share data, or not possible to obtain good quality translations of non-English reports by this time. The sensitivity analysis (Section 5.7.5) will incorporate aggregate data from studies lacking IPD.

5.6.4 MANAGEMENT OF INDIVIDUAL PATIENT DATA (IPD):

A copy of the raw data obtained from each study will be archived and saved in a restricted folder on receipt, prior to any modification of the data. Published statistics and analyses will be replicated where possible to identify the variables used, and to check the data to ensure accuracy and quality. Issues and discrepancies found will be raised and rectified with the study author. Individual study datasets will be reformatted to facilitate the merge across studies. Variables will be derived as required and the resulting dataset locked for analysis.

Datasets across studies will be merged for analysis. Where participant level outcomes and covariates have been measured on different scales, where possible these will be rescaled (e.g. *using the Z-score)* to standardize the measure, and if applicable, covariates will be centred on the mean for inclusion in subsequent modelling. Specific details of this process will be included in the analysis plan.

5.7 Data analysis:

5.7.1 STATISTICAL CONSIDERATIONS

A detailed analysis plan will be finalised by the statistical team and agreed by the full project team during project set-up, and subsequently approved by the collaborative group. Study data will not be used for any other purpose without the permission of collaborators.

Analyses will be conducted in accordance with current recommendations for IPD meta-analyses[31,32] and will consider appropriate adjustment for baseline covariates, handling of multiple treatment groups and control arms, missing data (outcome/patient/study levels and predictors of missing data), repeated measures, timing of outcomes, randomisation, within-study treatment-related clustering[33,34] and non-adherence.

Analysis populations for each analysis will be defined in the analysis plan and will be based on the intention-to-treat (ITT) principle, including all randomised participants regardless of withdrawal or protocol compliance.

5.7.2 DESCRIPTIVE ANALYSIS:

Study-level, arm-level, care-provider-level and participant-level characteristics of included studies will be summarised. We will compare these characteristics to those for studies that were eligible but did not supply IPD (using published sources), to determine if the IPD studies available are a representative and unbiased sample of all eligible studies. Funnel plots will be used to assess publication bias. Outcomes of included studies will be summarised, as will study- and adolescent-level moderators specified in subsequent analysis.

Missing data will be summarised, distinguishing between "systematically missing" (missing for all participants within a study) and "sporadically missing" data (incomplete data observed for at least some individuals within a study). We will assess missing data mechanisms by comparing characteristics of studies, patients (and clusters) with and without follow-up data.

5.7.3 DATA SYNTHESIS: ANALYSIS OF POOLED TREATMENT EFFECT

Objective 3.i: To provide updated estimates of the pooled treatment effect of any therapeutic intervention for self-harm compared to any non-active control in adolescents

All randomised participants and all trials will be included in the analyses of pooled treatment effect, of any therapeutic intervention compared to any non-active control, performed on an intention-to-treat basis. Analysis will be conducted for all primary and secondary outcomes:

Primary Outcome: Repetition of self-harm during follow-up. *Defined as a binary outcome over the maximum follow-up period within each trial, to a maximum 24 months.*

Secondary outcomes:

- Time to repetition of self-harm
- Presence (binary) and severity (continuous score) of general level of emotional and behavioural problems, for example SDQ or CBCL scores
- Presence (binary) and severity (continuous score) of Depression: Score on a self-report measure of depression
- Presence (binary) and severity (continuous score) of Suicidal ideation: Score on a self-report measure of Suicidal ideation
- Quality of Life: Score on a self-report Quality of Life scale
- Death of adolescent

Follow up: During analysis, studies including a follow-up assessment up to three months post-randomisation will be grouped to form a short-term follow-up, and any later assessment points will be grouped per six month period resulting in an analysis of follow-up outcomes in the short-term (up to 3 months), and at 6, 12, 18, and 24 months post-randomisation. Where studies include assessments beyond 24 months, these data will be included where feasible, and grouped as ≥24 months post-randomisation.

Effect measures:
Where outcomes comprise continuous data from the same scales, linear regression will be used to produce an estimate of the absolute mean difference in treatment effect. Where outcomes comprise continuous data from different scales, we will use linear regression to produce an estimate of the standardised mean difference in treatment effect, standardised according to the total standard deviation.

Where outcomes comprise binary data, logistic regression will be used to produce odds ratio

estimates of the effect of treatment; other effect measures (e.g. risk differences and relative risks) will also be considered to aid interpretation.

Where sufficient time to event data are available for outcomes repetition of self-harm and death, Cox proportional Hazards regression on censored time-to-event data will be used to produce hazard ratio estimates of the effect of treatment. Where data are available at specific time point's only, logistic regression on repeated measures time-to-event data will be used to produce odds ratio estimates of the effect of treatment. In both cases absolute differences will also be estimated from the model at relevant time points.

Analysis:

Where possible, primary results will be based on an one-stage IPD meta-analysis which analyses all patient-level data from all the trials in a single step simultaneously. Analysis will also be conducted using a two-stage approach to estimate the intervention effect in each study separately, followed by meta-analysis to pool aggregate results to ensure estimates are consistent and robust to possible convergence problems and modelling decisions.

For the dichotomous primary outcome of repetition of self-harm, we will use a logistic regression model, accounting for clustering of patients within studies as appropriate[33], and appropriately allowing for heterogeneity in baseline risk across studies, stratified by study in the one-stage analysis. The pooled treatment effect will be estimated using the random-effects approach, assuming a normal distribution of treatment effects across studies allowing for heterogeneity in treatment effect caused by different study characteristics. Estimation will use REML for both one and two-stage models, using a pseudo-likelihood approach for one-stage analysis of binary outcomes.

The model will adjust for key study level factors (e.g. follow-up duration, age of study, country, study quality) to control for sources of between-study heterogeneity in the outcome; those found to be important (at the 10% significance level) will be included in all subsequent IPD models.

We will report estimated treatment effects and 95% confidence intervals (appropriately adjusted for sampling errors in the estimated weights in the two-stage model) and inconsistency statistics. Heterogeneity will be assessed using the τ^2 statistic, the between-study variation from the one-stage meta-analysis, and the I^2 statistic (proportion of total variability due to between-study heterogeneity) from the two-stage meta-analysis. Forests plots with study-specific estimates of treatment effect, 95% confidence and prediction intervals will be presented based on the two-stage meta-analysis.

Where possible, we will use multiple imputation for missing data within studies, including predictors of missing data and treatment under the "missing at random" assumption to obtain less biased estimates from a more complete dataset[35,36]. We will also explore the possibility of publication bias and if detected use appropriate methods to account for it.

5.7.4 DATA SYNTHESIS: ANALYSIS BY ADOLESCENT-LEVEL CHARACTERISTICS

Objective 3.ii: To identify subgroups of adolescents in whom any therapeutic intervention is effective

Providing that there are sufficient data available, we will investigate whether the treatment effect is consistent across adolescent subgroups. These analyses will be carried out on the primary outcome, repeated for secondary outcomes, either where specified *a priori* in the statistical analyses plan or where evidence of subgroup effects are found on the primary

outcome to check for consistency across outcomes. Adolescent-subgroups will be included in analysis if they are represented in a sufficient number of trials; studies not collecting the moderator of interest will not be included in the specific analysis of their effect. Adolescent-subgroups will be pre-specified in the final analysis plan, agreed by the project management and collaborator group, and are likely to consist of:

- Age: <14, >14
- Age: As a continuous variable
- Sex: Male, Female
- Ethnicity: White, Other
- LGBT status: Identifies as LGBT or not
- ASD status: present, absent
- History of abuse: yes, no
- Presenting self-harm method: self-injury, self-poisoning, combined
- Number and timing of previous self-harm attempts: one, two, multiple
- Presence (binary) and severity (continuous score) of family dysfunction
- Presence (binary) and severity (continuous score) of comorbid psychiatric conditions (number of analyses limited by data availability but, in order of priority):
    - Depression
    - borderline personality disorder
    - unemotional/callous traits
    - eating disorders
    - anxiety disorders

We will extend the one- and two-stage models described in the analysis of pooled treatment effect (objective 3i) to investigate adolescent-level subgroup effects.

Where the number of studies contributing to the analysis allows we will account for clustering by study and treatment effects using random effects as per the primary analysis of the pooled treatment effect (3i), however fixed effects will be used otherwise.

We will include the adolescent-subgroup as a fixed main effect and fixed moderator-by-treatment interaction. Between-study heterogeneity in the within-study treatment-covariate interaction will also be measured, summarised and, if necessary, accounted for in the analysis.

In the one-stage model, centring of covariates around the mean value in each study, by including the mean and the different from this mean as separate terms, will ensure separation of within and across-study interaction effects to avoid ecological bias (ensuring that the interaction effect explains only the patient level variation in treatment response, not study level[37]).

IPD meta-analysis will increase the power to detect genuine sub-group effects. To ensure effects detected are not due to chance finding in a single study, subgroup effects will also be examined for consistency across studies, through estimates derived from the two-stage meta-analysis and presented in a forest plot. To account for multiple testing of moderators within the IPD meta-analysis, p-values will be subject to a stricter 1% level of significance for definitive conclusions, otherwise the 5% significance level will be retained to identify important trends and moderators to inform future research and at the study level (95% confidence intervals will be presented throughout).

5.7.5 DATA SYNTHESIS: ANALYSIS BY TRIAL LEVEL INTERVENTION CHARACTERISTICS

Objective 3.iii: To provide estimates of the pooled treatment effects of specific types of therapeutic intervention compared to any non-active control for self-harm in adolescents

The effect of therapeutic intervention may vary across trials in the meta-analysis because they each comprise different psychological or pharmacological interventions, or have applied interventions in different ways. Providing that there are sufficient data and studies available, analyses are planned whereby trials will be grouped into classes and by therapeutic modality. Groups will be pre-specified in the final analysis plan, agreed by the project management and collaborator group, and will likely consist of trials grouped according to whether the intervention comprised:

Class of intervention

- A group or individual targeted intervention
- A family or individual targeted intervention
- A service or participant (group/family/individual) targeted intervention
- Number of sessions
- Duration of treatment (in months)

Therapeutic modality

- A psychological therapeutic or pharmacological intervention
- Cognitive behavioural therapy or not
- Group therapy or not
- Dialectical Behaviour therapy or not
- Family therapy or not

For these trial groups, analyses will be carried out on the primary outcome, repeated for secondary outcomes, either where specified *a priori* in the statistical analyses plan or where evidence of subgroup effects are found on the primary outcome to check for consistency across outcomes.

Estimates of the pooled treatment effects of different trial-level intervention groups will be obtained through IPD meta-regression, extending the one- and two-stage models described in the analysis of pooled treatment effect (objective 3i) where possible and as appropriate. Study-level intervention groups will be included as fixed main effects and as fixed covariate-by-treatment interactions in order to estimate the across-study treatment interaction to investigate if there are any substantial differences in the effect of treatment between these trial groups. Forest plots depicting the individual study and pooled treatment effects for each group will be presented from the two-stage model.

Providing that there are sufficient data available, where two or more studies have evaluated a particular therapeutic intervention modality, we will further estimate the pooled treatment effect specific to the intervention, including only the studies evaluating the intervention (repeating the primary analysis model for objective 3i).

5.7.6 DATA SYNTHESIS: ANALYSIS BY ADOLESCENT-LEVEL AND TRIAL-LEVEL INTERVENTION CHARACTERISTICS

Objective 3.iv: To identify subgroups of adolescents for whom specific types of therapeutic

interventions for self-harm are effective

If substantial heterogeneity is detected between trial or treatment groupings, then providing sufficient data are available, adolescent-level subgroup analysis (objective 3ii) may also be conducted separately within trial groupings, to explore whether moderators are specific to certain therapeutic interventions.

Analysis will be based on the primary and secondary outcomes where appropriate, and carried out on subsets of trials according to their therapeutic intervention. Analysis will repeat the IPD meta-regression described for objective 3ii, investigating adolescent-level subgroup effects through inclusion as fixed main effects and moderator-by-treatment interactions, for the therapeutic intervention under investigation.

5.7.7 SENSITIVITY ANALYSES:

We will undertake a number of sensitivity analysis to test the robustness of our conclusions for the analysis of the primary outcome, repetition of self-harm. These will include methods for handling missing data[38], within-study clustering effects, non-adherence, and study quality.

Unavailable IPD data
Where IPD are not available or obtained for eligible studies, we will incorporate the mixture of aggregate data from studies lacking IPD (using published sources), and IPD for studies included in the main analysis in a two-step meta-analysis. The analysis will be conducted to explore the impact on estimates of the pooled treatment effects for any therapeutic intervention (objective 3.i) and specific types of interventions (objective 3.iii) and will also investigate funnel plot asymmetry[39] (potential publication bias). Similar analysis for objectives 3.ii and 3.iv, investigating subgroups of adolescents, will be dependent on availability of suitable aggregate data for adolescent subgroups.

6 Dissemination, Outputs and Anticipated Impact

6.1 Dissemination to the professional clinical and academic community

The advantage of creating a formal Collaborative Group of researchers who have published in this field is that we will be in regular communication with many of the leading experts in interventions for self-harm and we will use this group's networks and contacts to disseminate our findings to professional groups internationally.

We will create a project web site and post materials for professionals and users and carers on that site as they become available.
In addition, we will use more traditional means of dissemination to the clinical and academic community:

Formal peer review journal publications:
- The protocol will be registered on PROSPERO (https://www.crd.york.ac.uk/prospero/) and published in an open access journal, following PRISMA-P reporting guidelines (http://www.prismastatement.org/Extensions/Protocols.aspx)
- The systematic review and meta-analysis will be published in an open-access journal and be reported following PRISMA-IPD guidelines (http://www.prismastatement.org/Extensions/IndividualPatientData.aspx)

Academic conference presentations:
We will submit abstracts describing the results of the study to general child and adolescent mental health conferences, and more 'subject specific' conferences such as that run by the International Association for Suicide Prevention.

6.2 Dissemination to users and carers

We will work with our Service User Advisory Group and the Young Person's Mental Health Advisory Group to create user friendly and relevant materials for dissemination.

As recommended by our Service User Advisory Group we will create hashtags associated with the project and use social media to alert young people and their carers to the results of the project and signpost them to the project web site and to dissemination materials. As per their advice we will attempt to engage well known celebrities to share our message in order to increase our online visibility.

In addition, we will partner with organisations such as Childline and YoungMinds and ask that our results be posted on their web sites.

As also recommended by our Service User Advisory Group, if it does not lead to undue delay, we will endeavour to disseminate results during the national self-injury awareness day (01/03) with school assemblies and school posters dedicated to self-harm treatment.

7 Project / research timetable

<-3 months to 0 months: Pre-set-up: Continued recruitment to Collaborative group, continued protocol and related document development. Recruitment of the independent Study Steering Committee.
1 – 3 months: Set-up: Collaborative group and oversight groups confirmed, development of data collection forms and project databases. Finalise protocol and statistical analysis plan. Agree data transfer and sharing agreements First meeting of PMG and of SSC. First meeting of Collaborative group.
1-12 months: Literature searches and review. Confirmation of eligibility, quality assessment. Liaison with primary study authors to arrange secure transfer of data to Leeds CTRU. Data cleaning, manipulation and pre-analysis programming.
12-16 months: Meta-analysis and meta-regression as per pre-agreed analysis plan
16-18 months: Second meeting of Collaborative group. Final write up and dissemination. It is anticipated that dissemination will continue beyond the formal end of the grant.

8 Patient and Public Involvement

A formal Service User Advisory Group (SUAG) has been established comprising four young people, aged 14-16 who are current service users with a personal experience of self-harm. DO has responsibility for acting as the link with the SUAG.

Six 2-hour SUAG meetings will take place over the duration of the grant. To facilitate this

process and recognise the importance of the young people's input we will provide the young people with £20 worth of vouchers for their participation, travel reimbursements and refreshments during the meeting.

During the course of the study, we will also organise two meetings with the young people's parents using a similar format to that described for the young people.

The tasks envisaged for the SUAG will be:

- Continuing the process of education and familiarising the young people and their parents/ carers with the research methods proposed;
- Further discussion of the research questions, their importance and relevance, and ensuring that these reflect the needs and priorities of patients and the public;
- Reviewing and commenting on the progress of the research;
- Ensuring that all relevant subgroups of participants are investigated;
- Planning future PPI activities
- Reviewing the results of the research as they emerge and commenting on interpretation and relevance to young people and their parents/ carers;
- Helping write the plain English summary of the research outputs
- Helping disseminate the research outputs through social media, blogs, talks at conferences etc

Meetings with parents/ carers will have a similar agenda.

In addition to the SUAG activities, we will have up to two, 2-hour meetings towards the end of the project with the Young Person's Mental Health Advisory Group (YPMHAG) to focus on interpretation and dissemination of findings to young people and their families. The YPMHAG (https://ypmhag.org/) are hosted and funded by the Service User Research Enterprise (SURE) and the NIHR Maudsley Biomedical Research Centre (BRC) at South London and Maudsley NHS Foundation Trust and King's College London**.**

The YPMHAG are a group of 16-25 year olds with lived experience of using mental health services, or caring for someone who has used these services. It meets every six to eight weeks and invites researchers or research teams who would like advice and support to come and discuss projects. The Chief Investigator of this bid (DC) has worked successfully with YPMHAG before. We believe that given the complex nature of an Individual Patient Data meta-analysis, involvement of a group like this, who have considerable experience of research, in combination with our own SUAG who will meet us regularly, will help give us the best chance of explaining and disseminating our findings as clearly as is possible.

9 Governance

9.1 Ethics

Formal ethical approval for the project will be sought from the University of Leeds, Faculty of Medicine & Health Ethics Committee.

Formal collaboration agreements will be signed by all collaborating trialists that will include confirmation of the appropriate permissions to allow data sharing to take place. Data sharing and transfer will be subject to formal data sharing agreements signed by the University of Leeds and collaborating institutions.

9.2 Quality Assurance

The study will be conducted in accordance with current MRC Good Clinical Practice (GCP) guidelines, NHS Research Governance Framework and through adherence to Leeds CTRU Standard Operating Procedures (SOPs).

9.3 Confidentiality

All information collected during the course of the study will be kept strictly confidential.

The CTRU will comply with all aspects of the 2018 Data Protection Act, which incorporates the EU General Data Protection Regulation (GDPR).

Only analyses set out in an analysis plan that has been approved by Collaborating trialists will be conducted on shared data.

At the end of the study, original data sets provided by collaborating trialists destroyed and the study dataset securely archived at the CTRU for a minimum of 5 years.

10 Statement of Indemnity

This study is sponsored by the University of Leeds and the University of Leeds will be liable for negligent harm caused by the design of the study.

11 Study Organisation

The Chief Investigator (DC) has responsibility for overall co-ordination and leadership of the study, with day to day project management being the responsibility of a part time project manager within the Leeds Clinical Trials Research Unit.

The Project Management Group (PMG) comprising all applicants and the project manager will meet regularly to coordinate and oversee the delivery of the project plan.

A formal Collaborative Group of primary authors of included, eligible studies will be established and will meet twice but be actively involved in regular discussions related to accessing and interpreting data from their own studies.

A Study Steering Group (SSC) including independent clinical and statistical experts with relevant expertise and a PPI representative will provide independent oversight of the project.

12 Publication Policy

12.1 Authorship and acknowledgement

The success of the study depends upon the collaboration of all participants. For this reason,

credit for the main results will be given to all those who have collaborated in the study, through authorship and by contribution. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- final approval of the version to be published
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator, Co-Applicants, Project Manager and all collaborating data holders will be named as authors in any publication of the main study analyses, and an appropriate first author agreed through discussion amongst the Project Management Group (PMG) members.

The SSC will agree a publication plan and must be consulted prior to release or publication of any study data. The Chair and Independent members of the SSC will be acknowledged appropriately in study publications.

The NIHR HTA programme will be acknowledged in all publications as detailed below. Other key individuals will be included as authors or contributors as appropriate and at the discretion of the PMG. Any disputes relating to authorship will be resolved by the SSC.

12.2 Data source

Data from the CTRU database in Leeds must be used for data analyses for all abstracts and publications relating to the questions posed within the study protocol. Furthermore, the statistical team at the CTRU, with input from other co-applicants will perform all such analyses. If any additional analyses outside the remit of the protocol are to be performed, the statistical team at the CTRU should be involved.

12.3 Processes for the drafting, review and submission of abstracts and manuscripts

The agreed first author of any outputs is responsible for circulating these to the other members of the PMG for review at least 15 days prior to the deadline for submission.

The agreed first author of manuscripts is responsible for ensuring:
- timely circulation of all drafts to all co-authors during manuscript development and prior to submission
- timely (and appropriate) circulation of reviewers' comments to all co-authors
- incorporation of comments into subsequent drafts
- communication with the SSC (i.e. ensuring submission is in line with SSC publication
- plan, and ensuring SSC receive the final draft prior to submission)

The first author is responsible for submission of the publication and must keep the PMG and all authors informed of the abstract's or manuscript's status. The SSC will be kept informed of rejections and publications as these occur. On publication, the first author should send copies of the abstract or manuscript to the SSC, PMG, Study Sponsor and to all co-authors, and ensure communication with the NIHR HTA programme as outlined below.

In accordance with the NIHR HTA programme's requirements, all materials to be submitted for publication (written, audio/visual and electronic) should be sent to the NIHR at the time of submission or at least 28 days before the publication date, whichever is earlier. This applies to all publications regardless of whether or not the primary results have been published.

All publications must acknowledge NIHR HTA as the study's funding source and include an appropriate disclaimer regarding expressed views and opinions (example text is provided on the HTA website).

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Appendices

13.1 Appendix 1 Glossary of Terms

ASD	Autistic Spectrum Disorder
BRC	Biomedical Research Centre
CTRU	Leeds Clinical Trials Research Unit
EUnetHTA	European Network for Health Technology Assessment
GCP	MRC Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HTA	Health Technology Assessment
ICTRP	International Clinical Trials Registry Platform
IPD	Individual Patient Data
IG	Information Governance
ITT	Intention to Treat
LGBT	Lesbian, Gay, Bisexual, Transgender
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NSSI	Non-suicidal self-injury
PICO	Population, Intervention, Comparator, Outcomes
PMG	Project Management Group
QoL	Quality of Life
RCT	Randomised Controlled Trial
SASD	Statistical Analysis Software
SH	Self-harm
SHIFT	The Self-Harm Intervention: Family Therapy trial
SOP	Standard operating procedure
SSC	Study Steering Committee
SUAG	Service User Advisory Group
SURE	Service User Research Enterprise
UK	United Kingdom
US	United States
YPMHAG	Young Person's Mental Health Advisory Group

13.2 Appendix 2 Project Management Group Membership

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13.3 Appendix 3 SSC Terms of Reference

The role of the SSC is to provide overall supervision for a project on behalf of the Project Sponsor and Project Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice.

The day-to-day management of the project is the responsibility of the Chief Investigator, and as such the Chief Investigator may wish to set up a separate Project Management Group (PMG) to assist with this function.

The main features of the SSC are as follows:

- To provide advice, through its Chair, to the Trial/Project Funder, the Trial/Project Sponsor, the Chief Investigator, the Host Institution and the Contractor on all appropriate aspects of the project
- To concentrate on progress of the trial/project, adherence to the protocol, patient safety (where appropriate) and the consideration of new information of relevance to the research question
- To ensure appropriate ethical and other approvals are obtained in line with the project plan
- To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
- To provide advice to the investigators on all aspects of the trial/project.

Constitution of the SSC
- The relevant NIHR Programme Director will review the nominees and appoint the Chair and members
- All SSC meetings are to have a minimum of 75% majority of independent members
- The minimum quoracy for a meeting to conduct business is 67% of appointed members
- Only appointed members will be entitled to vote, and the Chair will have a casting vote
- The Chair and members to sign and maintain a log of potential conflicts and/or interests
- Attendance at SSC meetings by non-members is at the discretion of the Chair
- The primary SSC reporting line is via the Chair to the relevant NIHR Programme Director; however, communication is likely to be between the Chair and the NIHR Research Manager who has day to day responsibility for the project.

Composition of the SSC
- An Independent Chair (UK based and/or holding a substantive UK based appointment)
- Independent statistician, health economist and clinician(s) and any others with expertise relevant to the project
- At least one individual who is able to contribute a patient and/or wider public perspective Ideally, the SSC should invite observers, including a representative of the sponsor and a representative from the research network to meetings

SSC meetings
Although there may be periods when more frequent meetings are necessary, the SSC should meet at least annually. Minutes of meetings should be sent to all members, the sponsor, and the funder and be retained in the study master file.

The responsibility for calling and organising SSC meetings lies with the Chief Investigator, in association with the Chair.

The Role of the Chair of SSC

The Chair of the SSC is directly answerable to the relevant NIHR programme, as funder.

The Chair's responsibilities include:

- Liaising with the Chief Investigator to arrange a meeting to finalise the protocol and to set up a schedule of meetings to align with the project plan
- Establishing clear reporting lines – to the Funder, Sponsor, etc.
- Being familiar with relevant guidance documents if appropriate
- Providing an independent, experienced opinion if conflicts arise between the needs of the research team, the funder, the sponsor, the participating organisations and/or any other agencies
- Leading the SSC to provide regular, impartial oversight of the study, especially to identify and pre-empt problems
- Ensuring that changes to the protocol are debated and endorsed by the SSC; letters of endorsement should be made available to the project team when requesting approval from the funder and sponsor for matters such as changes to protocol
- Being available to provide independent* advice as required, not just when SSC meetings are scheduled
- Commenting on any extension requests and, where appropriate, providing a letter to the funder commenting on whether the extension request is supported or otherwise by the independent members of the SSC
- Commenting in detail (when appropriate) regarding the continuation, extension or termination of the project.

13.4 Appendix 4: Systematic Review Search Strategy

(search updated 21/06/19 – added meta-regression terms)

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to June 20, 2019>
Search Strategy:
---
1 Self-Injurious Behavior/ (7200)
2 suicide/ or suicide, attempted/ (51983)
3 Drug Overdose/ (10369)
4 Self Mutilation/ (3180)
5 (selfharm* or selfinjur* or selfinflict* or "self harm*" or "self injur*" or "self inflict*").ti. (4978)
6 ((self or themsel* or onesel*) adj2 (aggress* or harm* or cutt* or immolat* or inflict* or injur* or mutilat* or poison* or damag* or destruct*)).ti. (7491)
7 (auto adj (aggress* or mutilat*)).ti. (75)
8 (automutilat* or "auto mutilation*" or autoaggress* or "auto agress*").ti. (222)
9 suicid*.ti. (40905)
10 (parasuicid* or para-suicid*).ti. (332)
11 ((deliberat* or intentional or intended) adj2 (overdos* or poison* or self poison*)).ti. (413)
12 (poison adj2 (deliberat* or intentional or intended)).ti. (3)
13 (overdos* adj2 (deliberat* or intentional or intended)).ti. (138)
14 NSSI.ti. (52)
15 (headbang* or head-bang*).ti. (70)
16 or/1-15 (80097)
17 Adolescent/ (1939543)
18 (teenage* or adolescen* or youth).tw. (304577)
19 young adult/ (749895)
20 (young* adj (people* or person* or adult* or m?n or wom?n)).tw. (173989)
21 child/ (1620458)
22 (school* adj2 (pupil* or student*)).tw. (20810)
23 (("11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj (yr? or year?)).tw. (471642)
24 (("11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj4 (old or age?)).tw. (618630)
25 (teen or teens or juvenil*).tw. (87194)
26 or/17-25 (3594742)
27 and/16,26 (28777)
28 ((systematic adj2 review*) or meta-analys* or "meta analysis" or "meta-regression" or "meta regression").ti. (162612)
29 limit 27 to (meta analysis or "systematic review") (290)
30 27 and 28 (271)
31 29 or 30 [srs + self harm+ adolescents] (346)

Database: Embase Classic+Embase <1947 to 2019 June 20>
Search Strategy:
---
1 *automutilation/ (7762)
2 *suicide/ or *suicide, attempt/ (40508)
3 *Drug Overdose/ (9293)
4 (selfharm* or selfinjur* or selfinflict* or "self harm*" or "self injur*" or "self inflict*").ti. (5763)

5 ((self or themsel* or onesel*) adj2 (aggress* or harm* or cutt* or immolat* or inflict* or injur* or mutilat* or poison* or damag* or destruct*)).ti. (8760)
6 (auto adj (aggress* or mutilat*)).ti. (75)
7 (automutilat* or "auto mutilation*" or autoaggress* or "auto agress*").ti. (292)
8 suicid*.ti. (48944)
9 (parasuicid* or para-suicid*).ti. (418)
10 ((deliberat* or intentional or intended) adj2 (overdos* or poison* or self poison*)).ti. (535)
11 (poison adj2 (deliberat* or intentional or intended)).ti. (4)
12 (overdos* adj2 (deliberat* or intentional or intended)).ti. (191)
13 NSSI.ti. (56)
14 (headbang* or head-bang*).ti. (86)
15 or/1-14 (74633)
16 Adolescent/ (1577703)
17 (teenage* or adolescen* or youth).tw. (406857)
18 young adult/ (295046)
19 (young* adj (people* or person* or adult* or m?n or wom?n)).tw. (240389)
20 child/ (1862127)
21 (school* adj2 (pupil* or student*)).tw. (25707)
22 (teen or teens or juvenil*).tw. (113717)
23 (("11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj4 (old or age?)).tw. (989096)
24 (("11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj (yr? or year?)).tw. (750109)
25 or/16-24 [Adolescents] (3888109)
26 15 and 25 (20956)
27 ((systematic adj2 review*) or meta-analys* or "meta analysis" or "meta-regression" or "meta regression").ti. (199945)
28 limit 26 to (meta analysis or "systematic review") (276)
29 26 and 27 (189)
30 28 or 29 [SRs + Self Harm + Adolescents] (322)

Database: PsycINFO <1806 to June Week 2 2019>
Search Strategy:
---
1 *Self-Injurious Behavior/ (3109)
2 *suicide/ or ATTEMPTED SUICIDE/ (29252)
3 *Drug Overdoses/ (1341)
4 *Self-Mutilation/ (1006)
5 (selfharm* or selfinjur* or selfinflict* or "self harm*" or "self injur*" or "self inflict*").ti. (4830)
6 ((self or themsel* or onesel*) adj2 (aggress* or harm* or cutt* or immolat* or inflict* or injur* or mutilat* or poison* or damag* or destruct*)).ti. (6406)
7 (auto adj (aggress* or mutilat*)).ti. (18)
8 (automutilat* or "auto mutilation*" or autoaggress* or "auto agress*").ti. (30)
9 suicid*.ti. (33008)
10 (parasuicid* or para-suicid*).ti. (346)
11 ((deliberat* or intentional or intended) adj2 (overdos* or poison* or self poison*)).ti. (114)
12 (poison adj2 (deliberat* or intentional or intended)).ti. (3)
13 (overdos* adj2 (deliberat* or intentional or intended)).ti. (20)
14 NSSI.ti. (65)
15 (headbang* or head-bang*).ti. (43)
16 or/1-15 (43517)

17 (teenage* or adolescen* or youth).tw. (302025)
18 (young* adj (people* or person* or adult* or m?n or wom?n)).tw. (94804)
19 (school* adj2 (pupil* or student*)).tw. (68733)
20 (("11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj (yr? or year?)).tw. (154851)
21 (("11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj4 (old or age?)).tw. (271489)
22 (teen or teens or juvenil*).tw. (36683)
23 or/17-22 (647709)
24 and/16,23 (13081)
25 ((systematic adj2 review*) or meta-analys* or "meta analysis" or "meta-regression" or "meta regression").ti. (30089)
26 limit 24 to (meta analysis or "systematic review") (164)
27 24 and 26 (164)
28 26 or 27 (164)

Cochrane Database of Systematic Reviews

Issue 6 of 12, June 2019

ID Search Hits
#1 MeSH descriptor: [Self-Injurious Behavior] this term only 271
#2 MeSH descriptor: [Suicide] this term only 601
#3 MeSH descriptor: [Suicide, Attempted] this term only 360
#4 MeSH descriptor: [Drug Overdose] this term only 127
#5 MeSH descriptor: [Self Mutilation] this term only 33
#6 (selfharm* or selfinjur* or selfinflict* or "self harm*" or "self injur*" or "self inflict*"):ti 284
#7 ((self or themsel* or onesel*) near/2 (aggress* or harm* or cutt* or immolat* or inflict* or injur* or mutilat* or poison* or damag* or destruct*)):ti379
#8 (auto near/2 (aggress* or mutilat*)):ti 4
#9 (automutilat* or "auto mutilation*" or autoaggress* or "auto agress*"):ti 4
#10 suicid*:ti 1481
#11 (parasuicid* or para-suicid*):ti 31
#12 ((deliberat* or intentional or intended) near/2 (overdos* or poison* or self poison*)):ti 79
#14 (overdos* or poison):ti 222
#15 NSSI:ti 0
#16 (headbang* or head-bang*):ti 0
#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 2423
#18 MeSH descriptor: [Adolescent] this term only 99786
#19 (teenage* or adolescen* or youth) 134000
#20 MeSH descriptor: [Young Adult] this term only 218
#21 (young* adj (people* or person* or adult* or m?n or wom?n)) 1132
#22 MeSH descriptor: [Child] this term only 1093
#23 (school* adj2 (pupil* or student*)).tw. 9485
#24 (("11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj (yr? or year?)).tw. 9484
#25 (("11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj4 (old or age?)) 354
#26 (teen or teens or juvenil*) 4791
#27 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #26 143881
#28 #17 and #27 730
Limit to Cochrane Database of Systematic Reviews 8

EPISTEMONIKOS

(advanced_title_en:(advanced_title_en:(advanced_title_en:(advanced_title_en:(Self-Injurious Behavior)) OR advanced_title_en:(suicid*) OR advanced_title_en:(Drug Overdose) OR advanced_title_en:((selfharm* OR selfinjur* OR selfinflict* OR "self harm*" OR "self injur*" OR "self inflict*").) OR advanced_title_en:(((self OR themsel* OR onesel*) AND (aggress* OR harm* OR cutt* OR immolat* OR inflict* OR injur* OR mutilat* OR poison* OR damag* OR destruct*)).)) OR advanced_title_en:((automutilat* OR "auto mutilation*" OR autoaggress* OR "auto agress*")) OR advanced_title_en:((parasuicid* OR para-suicid*)) OR advanced_title_en:(((deliberat* OR intentional OR intended) AND (overdos* OR poison* OR self poison*))) OR advanced_title_en:((poison AND (deliberat* OR intentional OR intended))) OR advanced_title_en:((overdos* AND (deliberat* OR intentional OR intended)).) OR advanced_title_en:(NSSI) OR advanced_title_en:((headbang* OR head-bang*))) OR
advanced_abstract_en:(advanced_title_en:(advanced_title_en:(advanced_title_en:(Self-Injurious Behavior)) OR advanced_title_en:(suicid*) OR advanced_title_en:(Drug Overdose) OR advanced_title_en:((selfharm* OR selfinjur* OR selfinflict* OR "self harm*" OR "self injur*" OR "self inflict*").) OR advanced_title_en:(((self OR themsel* OR onesel*) AND (aggress* OR harm* OR cutt* OR immolat* OR inflict* OR injur* OR mutilat* OR poison* OR damag* OR destruct*)).)) OR advanced_title_en:((automutilat* OR "auto mutilation*" OR autoaggress* OR "auto agress*")) OR advanced_title_en:((parasuicid* OR para-suicid*)) OR advanced_title_en:(((deliberat* OR intentional OR intended) AND (overdos* OR poison* OR self poison*))) OR advanced_title_en:((poison AND (deliberat* OR intentional OR intended))) OR advanced_title_en:((overdos* AND (deliberat* OR intentional OR intended)).) OR advanced_title_en:(NSSI) OR advanced_title_en:((headbang* OR head-bang*)))) AND (advanced_title_en:((teenage* OR adolescen* OR youth OR young OR pupil OR student OR schoolchild OR child OR teen* OR juvenil*) OR (("11" OR "12" OR "13" OR "14" OR "15" OR "16" OR "17" OR "18" OR "19") AND (year? OR yr? OR old OR age?)).) OR advanced_abstract_en:((teenage* OR adolescen* OR youth OR young OR pupil OR student OR schoolchild OR child OR teen* OR juvenil*) OR (("11" OR "12" OR "13" OR "14" OR "15" OR "16" OR "17" OR "18" OR "19") AND (year? OR yr? OR old OR age?)).)) [Filters: classification=systematic-review, protocol=no] 392

PROSPERO: International prospective register of systematic reviews

#1	MeSH DESCRIPTOR Suicide, Attempted	76
#2	MeSH DESCRIPTOR Suicide	190
#3	MeSH DESCRIPTOR Self-Injurious Behavior	91
#4	MeSH DESCRIPTOR Self Mutilation	0
#5	selfharm* or selfinjur* or selfinflict* or "self harm*" or "self injur*" or "self inflict*":TI	72
#6	((self or themsel* or onesel*) adj2 (aggress* or harm* or cutt* or immolat* or inflict* or injur* or mutilat* or poison* or damag* or destruct*)) :TI	78
#7	(auto adj (aggress* or mutilat*)):TI	0
#8	suicid* or parasuicid* or para-suicid*:TI	256
#9	(automutilat* or "auto mutilation*" or autoaggress* or "auto agress*"):TI	6
#10	overdos* or poison*:TI	44
#11	NSSI	3
#12	headbang* or head-bang*	0
#13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	356
#14	MeSH DESCRIPTOR Adolescent	1686
#15	MeSH DESCRIPTOR Young adult	195
#16	MeSH DESCRIPTOR Child	3884
#17	teenage* or adolescen* or youth or young or teen or teens or juvenil*	7962

#18	(school* adj2 (pupil* or student*))	1424
#19	#14 OR #15 OR #16 OR #17 OR #18	15151
#20	#15 AND #21	123

13.5 Appendix 5: RCT Search Strategy

Database: Ovid MEDLINE(R) <1946 to July Week 1 2019>

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1 Self-Injurious Behavior/ (7216)
2 suicide/ or suicide, attempted/ or suicide, assisted/ (57157)
3 Drug Overdose/ (10403)
4 Self Mutilation/ (3181)
5 (selfharm* or selfinjur* or selfinflict* or "self harm*" or "self injur*" or "self inflict*").ti. (4170)
6 ((self or themsel* or onesel*) adj2 (aggress* or harm* or cutt* or immolat* or inflict* or injur* or mutilat* or poison* or damag* or destruct*)).ti. (6433)
7 (auto adj (aggress* or mutilat*)).ti. (73)
8 (automutilat* or "auto mutilation*" or autoaggress* or "auto agress*").ti. (219)
9 suicid*.ti. (36367)
10 (parasuicid* or para-suicid*).ti. (323)
11 ((deliberat* or intentional or intended) adj2 (overdos* or poison* or self poison*)).ti. (368)
12 (poison adj2 (deliberat* or intentional or intended)).ti. (3)
13 (overdos* adj2 (deliberat* or intentional or intended)).ti. (120)
14 NSSI.ti. (35)
15 (headbang* or head-bang*).ti. (65)
16 or/1-15 [self harm] (77902)
17 Adolescent/ (1942456)
18 (teenage* or adolescen* or youth).tw. (261364)
19 young adult/ (753275)
20 (young* adj (people* or person* or adult* or m?n or wom?n)).tw. (151441)
21 child/ (1622676)
22 (school* adj2 (pupil* or student*)).tw. (17529)
23 (("11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (yr? or year?)).tw. (518089)
24 (("11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj4 (old or age?)).tw. (544703)
25 (teen or teens or juvenil*).tw. (77115)
26 or/17-25 [adolescents] (3474833)
27 and/16,26 [self harm and adolescents] (27664)
28 randomized controlled trial.pt. (484695)
29 controlled clinical trial.pt. (93122)
30 randomized.ab. (387592)
31 placebo.ab. (180613)
32 clinical trials as topic.sh. (187532)
33 randomly.ab. (268249)
34 trial.ti. (172865)
35 28 or 29 or 30 or 31 or 32 or 33 or 34 (1107251)
36 exp animals/ not humans.sh. (4595710)
37 35 not 36 [Cochrane RCT precision maximising search filter] (1008831)
38 27 and 37 (1111)
39 limit 38 to english language (1058)
40 38 not 39 (53)
41 limit 38 to yr="2016 -Current" (213)
42 40 or 41 (263)

PsycINFO <1806 to August Week 1 2019>

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1 Self-Injurious Behavior/ (3704)
2 suicide/ or ATTEMPTED SUICIDE/ (32401)
3 Drug Overdoses/ (1603)
4 Self-Mutilation/ (1134)
5 (selfharm* or selfinjur* or selfinflict*).tw,id. (41)
6 ((self or themsel* or onesel*) adj2 (aggress* or harm* or cutt* or immolat* or inflict* or injur* or mutilat* or poison* or damag* or destruct*)).tw,id. (19309)
7 (automutilat* or "auto mutilat*" or auto-mutilat*).tw,id. (38)
8 (autoaggress* or "auto aggress*" or auto-aggress).tw,id. (179)
9 suicidality.tw,id. (6757)
10 (parasuicid* or para-suicid*).tw,id. (769)
11 (suicid* adj2 (attempt* or behavio* or intent* or intend* or commit*)).tw,id. (25780)
12 (suicid* adj2 (death or die* or morality or complete)).tw,id. (2815)
13 (poison adj2 (deliberat* or intentional or intended)).tw,id. (5)
14 (overdos* adj2 (deliberat* or intentional or intended)).tw,id. (98)
15 NSSI.tw,id. (1211)
16 or/1-15 (59726)
17 (teenage* or adolescen* or youth or child*).tw,id. (861956)
18 (young* adj (people* or person* or adult* or m?n or wom?n)).tw,id. (95755)
19 (school* adj2 (pupil* or student*)).tw,id. (69089)
20 (("11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj4 (old or age?)).tw,id. (273131)
21 (teen or teens or juvenil*).tw,id. (36904)
22 or/17-21 (1092645)
23 and/16,22 (21443)
24 exp clinical trials/ or experimental design/ (22302)
25 exp treatment effectiveness evaluation/ (23746)
26 exp mental health program evaluation/ (2073)
27 exp random sampling/ (822)
28 randomi*.tw. (80868)
29 (clinic* adj4 trial*).tw. (35605)
30 (random* adj5 (assign* or allocat* or assort*)).tw. (42633)
31 (crossover or cross-over).tw. (9853)
32 ((singl* or doubl* or tripl* or trebl*) adj (blind* or mask*)).tw. (25295)
33 exp placebo/ (5306)
34 placebo*.tw. (39404)
35 or/24-34 [Trials] (187653)
36 23 and 35 (829)
37 limit 36 to yr="2015 -Current" (220)

13.6 Appendix 6: Studies from scoping review and key published reviews meeting RISA-IPD eligibility criteria

Study	Year	Country	N	Age	Intervention	Control	Self-harm reported as outcome	Follow-up length (months)
Studies meeting eligibility criteria. All participants to be included in RISA-IPD								
Asarnow[40]	2017	US	42	11-18	CBT/ DBT informed family management	*TAU + Parent support	Yes	12
Cotgrove[41]	1995	UK	105	<16	Token plus assessment as usual	Assessment as usual	Yes	12
Cottrell[19]	2018	UK	832	11-17	Family therapy	TAU	Yes	18
Donaldson[42]	2005	US	39	12-17	Skills based treatment	Supportive treatment	Yes	6
Green[43]	2011	UK	366	12-17	Group therapy plus TAU	TAU	Yes	12
Hazell[44]	2009	Australia	72	12-16	Group therapy plus TAU	TAU	Yes	12
Mehlum[45]	2016	Norway	77	12-18	Brief **DBT	Enhanced TAU	Yes	18
Ougrin[46]	2013	UK	70	12-18	Therapeutic Assessment	Assessment as usual	Yes	24
Rossouw[47]	2012	UK	80	12-17	Mentalisation based treatment	TAU	Yes	12
Spirito[48]	2002	US	76	12-18	Problem Solving	TAU	Yes	3
Wood[49]	2001	UK	63	12-16	Group therapy plus TAU	TAU	Yes	7
Studies partially meeting eligibility criteria, not all self-harmed prior to randomisation. Eligible participants to be included in RISA-IPD								
Asarnow[50]	2011	US	181	10-18	Family based CBT	TAU	Yes	2
Chanen[51]	2008	Australia	86	15-18	Cognitive Analytic Therapy	TAU	Yes	24
Esposito[52]	2011	US	40	13-17	CBT	Enhanced TAU	Yes	18

Huey[53]	2004	US	156	10-17	MST	Hospitalisation	Yes	12
King[54]	2006	US	289	12-17	Youth nominated Support plus TAU	TAU	Yes	6
King[55]	2009	US	448	13-17	Youth nominated Support v2, plus TAU	TAU	Yes	12
Pineda[56]	2013	Australia	48	12-17	Interactive psycho-education for parents plus TAU	TAU	Yes	6
Studies partially meeting eligibility criteria, not all participants aged 11-18. Some participants to be included in RISA-IPD								
Cooney[57]	2010	NZ	29	13-19	DBT	TAU	Yes	18
McLeavey[58]	1994	Ireland	39	15-45	Interpersonal Problem Solving	Brief problem-oriented approach	Yes	6
Robinson[59]	2012	Australia	164	15-24	Postcard plus TAU	TAU	Yes	18
Slee[60]	2008	Holland	90	15-35	CBT plus TAU	TAU	Yes	9

* TAU = Treatment as Usual
** DBT = Dialectical Behaviour Therapy
*** CBT = Cognitive Behavioural Therapy