The Clinical and cost-effectiveness of an exercise intervention for depression in adolescents: a phased, multi-site randomised controlled trial.

Short title: A Randomised controlled trial of energetic activity for depression in young people – The READY Trial.

Feasibility Phase Study Protocol

Short title: The READY Trial

Version number: 3.0 27th May 2021

Funder: National Institute for Health Research, Health Technology Assessment Programme

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Sponsors: University of Hertfordshire (UH)

Sponsor Number:

Clinical trial registration number: ISRCTN66452702

IRAS reference number: 276093

UH Protocol Number: aLMS/SF/UH/02955(1)

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General information

This document provides details regarding the setting up of, conduct, analysis and dissemination of the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) funded study (HTA ref: 17/78/10), *The clinical and cost-effectiveness of an exercise intervention for depression in adolescents: a phased, multi-site randomised controlled trial (A randomised controlled trial of energetic activity for depression in young people – The READY Trial).*

The University of Hertfordshire (UH) will sponsor this study. Hertfordshire Partnership NHS University Foundation Trust, Norwich Clinical Trials Unit at the University of East Anglia, Norfolk and Suffolk NHS Foundation Trust, East London NHS Foundation Trust and the University of Bedfordshire will be collaborators in the study. As such, a collaboration agreement will be signed by the parties, specifying responsibilities and financial arrangements.

Chief Investigator	Dr Daksha Trivedi and Dr David Wellsted
Academic Lead	Dr Daksha Trivedi and Dr David Wellsted
Trial Co-ordinator	Ms Claire Rourke
Sponsors	University of Hertfordshire
Committees	Trial Steering Committee Trial Management Group Data Monitoring and Ethics Committee Young People's Advisory Group Stakeholder Forum

Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigators agree to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Good Clinical Practice (GCP) guidelines, the Sponsor's (and any other relevant) Standard Operating Procedures (SOPs), and other regulatory requirements as amended.

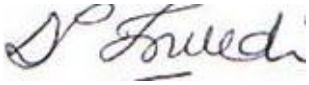
We agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

We also confirm that we will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

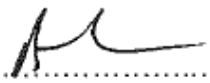
Name: David Wellsted Role: *Chief investigator*

Signature: …  … Date: 27/01/2020.

Name: Daksha Trivedi Role: *Chief investigator*

Signature:  Date: 27/01/2020

Name: ALLAN CLARK. Role: *Statistician*

Signature:  Date: 27/1/20

Name: **Professor John Senior** Role: *Sponsor*

31.01.2020

Signature: …… Date: ……

Abbreviations and key terminology

Organisations and personnel involved in the delivery of the study:

CI	Chief Investigator
ELFT	East London NHS Foundation Trust
HPFT	Hertfordshire Partnerships NHS University Foundation Trust (HPFT)
NCTU	Norwich Clinical Trials Unit
NSFT	Norfolk and Suffolk NHS Foundation Trust
UoB	University of Bedfordshire
UEA	University of East Anglia
UH	University of Hertfordshire

The University of Hertfordshire will sponsor the programme of work. The Co-CIs will be responsible for delivery of the project

Further abbreviations and definitions:

AE	Adverse Event
A&E	Accident and Emergency
APR	Annual progress report
BAME	Black Asian and Minority Ethnicity
BCT	Behaviour Change Techniques
BSFC-s	Burden Scale for Family Caregivers – short form
CAMHS	Child and Adolescent Mental Health Services
CBT	Cognitive Behavioural Therapy
CI	Chief Investigator
CDI	Clinical Depression Inventory
CHU-9D	Child Health Utility 9D
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTU	Clinical Trials Unit
CTSN	Clinical Trials Support Network
CRN	Clinical Research Network
CSRI	Client Service Receipt Inventory
DMEC	Data Monitoring and Ethics Committee
DSM 5	Diagnostic statistical manual of mental disorders, version 5
DAWBA	Development and Well-Being Assessment
EQ-VAS	EuroQol Visual Analogue Scale
GCP	Good Clinical Practice
HIIT	High Intensity Interval Training
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
LGBTQ	Lesbian, Gay, Bisexual, Transsexual, Queer
LTP	Local Transformation Plan
MHSW	Mental Health Support Worker

MSPSS	Multidimensional Scale of Perceived Social Support
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NETSCC	NIHR Evaluation Trials and Studies Co-ordinating Centre
OARS	Open-ended questions, Affirmations, Reflective listening, Summaries
PANAS	Positive and Negative Affect Schedule
PAR-Q	Physical Activity Readiness Questionnaire
PI	Principal Investigator
PIC	Participant Identification Centre
PID	Participant identifier
PIRg	Public Involvement in Research Group
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QA	Quality Assurance
QC	Quality Control
QALY	Quality Adjusted Life Year
QMMP	Quality Management and Monitoring Plan
RCT	Randomised Controlled Trial
RDS	Research Design Service
REC	Research Ethics Committee
REP	Registered Exercise Professionals
R&D	Research & Development Department
RULE	Resist the righting reflex; Understand your client's motivation; Listen to your client; Empower your client)
SAE	Serious Adverse Event
SDQ	Strengths and Difficulties Questionnaire
SPA	Single Point of Access
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SRE	Serious Related Event
SOP	Standard Operating Procedure
SW	Support Workers
TIDieR	Template for Intervention Description and Replication
TDF	Theoretical Domains Framework
TMG	Trial Management Group
TMF	Trial Master File
TSC	Trial Steering Group
Y-PAQ	Youth Physical Activity Questionnaire
UK	United Kingdom

Trial summary

Trial title	The Clinical and cost-effectiveness of exercise intervention for depression in adolescents: a phased, multi-site randomised controlled trial (A Randomised controlled trial of energetic activity for depression in young people – feasibility phase).
Short title	A randomised controlled trial of energetic activity for depression in young people – The READY Trial
Clinical Trial Registration No.	ISRCTN66452702
IRAS Reference number	276093
UH Protocol number	aLMS/SF/UH/02955(1)
Funder	Health Technology Assessment arm of the National Institute for Health Research (NIHR)
Contact for Information	d.trivedi@herts.ac.uk d.m.wellsted@herts.ac.uk
Trial Design	Feasibility of a multi-site, three arm cluster RCT
Trial Participants	Young people aged 13-17 years with mild to moderate depression Inclusion criteria: ● Help-seeking adolescents aged 13-17 years with a Clinical Depression Inventory (CDI) 2 score between 17 and 36, inclusive (mild to moderate symptoms). ● Current treatment with antidepressants or other drug, or psychological therapy is allowed ● Young person consent to participate, with consent from parent/carer for under 16s and consent of parent/carer to provide data ● Parent/carer/guardian also taking part in the study ● Young person and parent/carer is able to complete the questionnaires in English ● Young person able to attend the intervention session Exclusion criteria: ● Considered unsuitable by the referring clinician ● Current treatment, or co-morbid conditions present contraindications to engaging in Randomised Controlled Trial (RCT) or exercise ● Active psychosis, significant substance abuse, self-harm, or suicidal ideation presenting significant risk (assessed as part of the Development and Well-Being Assessment (DAWBA))
Planned Sample Size	Eighty-one individuals: 27 in each arm, evenly distributed across the three sites The recruitment period is twelve months
Intervention	Up to 57 minutes of physical exercise (1) high intensity exercise, or (2) low intensity exercise and behaviour change session, twice a week over a 12-week period
Comparison	Forty-five minutes of social non-exercise activities and behaviour change session, twice a week over a 12-week period
Follow up duration	Fourteen weeks and six months post-randomisation

Planned Trial Period	Eighteen months
Study objectives	To establish the feasibility and acceptability of conducting a full RCT including an embedded process evaluation with user and stakeholder input at three sites (Hertfordshire, Norfolk and Bedfordshire). The trial will determine whether it is possible to recruit young people to the trial, deliver the intervention as planned, evaluate the training and delivery of the intervention, and provide data to inform the design of the main trial.
Outcomes	● Referral, recruitment and retention ● Attendance at intervention sessions ● Heart rate, physical activity ● Adherence to the intervention protocol ● Proportions of missing data in each of the outcomes for the RCT ● Adverse events ● Resource use – performance of data collection methods for the economic evaluation ● Reach and representativeness

Roles and responsibilities of individuals and committees

Protocol contributors

All contributed to specific areas of the study design and protocol development relative to their expertise. All applicants approved the final submission of the funding proposal and the protocol and are the grant holders.

Name	Affiliation	Role
Dr Daksha Trivedi	UH	Joint Chief Investigator. Designed the framework for the study and wrote the first draft of the funding application.
Dr David Wellsted	UH	Joint Chief Investigator. Designed the framework for the study and wrote the first draft of the funding application.
Dr Jon Wilson	NSFT	Principal Investigator at NSFT/UEA and project clinical oversight. Provided clinical and research expertise to the study design.
Dr Lindsay Bottoms	UH	Contributed to the intervention and delivery components.
Dr Angel Chater	UoB	Contributed to the behaviour change, intervention and delivery components.
Dr Allan Clark	UEA	Study Statistician. Provided statistical input.
Dr Tim Clarke	NSFT	Contributed clinical expertise.
Dr Lee David		Contributed clinical expertise.
Dr Neil Howlett	UH	Contributed to the behaviour change, intervention and delivery components.
Dr Karen Irvine	UH	Drafted the initial version and co-ordinated development of the protocol.
Prof Andy Jones	UEA	Contributed to the intervention and delivery components.
Dr Julia Jones	UH	Patient and Public Involvement (PPI) Lead. Drafted the PPI strategy and initial literature review.
Dr Silvana Mengoni	UH	Process evaluation expertise.
Dr Jamie Murdoch	UEA NCTU	Process evaluation expertise.
Mr Martin Pond	UEA NCTU	Data Management design and delivery.
Dr Shivani Sharma	UH	Provided expertise on engaging with hard to reach groups in research.
Dr Erika Sims	UEA NCTU	Provided operational advice for set-up, delivery and close-down of the feasibility study and transition to full-trial.
David Turner	UEA	Health Economist. Provided economic health analysis components.
Solange Wyatt	UH	Provided clinical trials expertise including governance, data management and contracting

Other key study personnel

- Trial Manager
- Research Assistant – Participant recruitment and data collection
- Data Manager
- Registered Exercise Professionals
- Mental Health Support Workers

Trial Steering Committee

The Trial Steering Committee (TSC) will meet three times a year and will provide overall supervision for the study on behalf of the Project Sponsor and the Project Funder. It will ensure that the study 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 (GCP). The TSC will operate according to NIHR Evaluation Trials and Studies Co-ordinating Centre (NETSCC) Project Oversight Groups Guidance. Members of the Young People's Advisory Group (YPAG), parents or carers, and the Public Involvement in Research group (PIRg) will join the TSC. Details of membership of the TSC and its Terms of Reference (ToR) will be held on the Trial Master File (TMF).

Data Monitoring and Ethics Committee

The Data Monitoring and Ethics Committee (DMEC) will monitor the study data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue. It is responsible for ensuring that the safety, rights and well-being of the trial participants remain paramount. It will consider the need for any interim analysis and advise the TSC regarding the release of data and/or information.

Full details of the roles and responsibilities of the DMEC including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the READY DMEC ToR, a copy of which is held on the TMF.

Responsibility for convening DMEC meetings lies with the Chief Investigator (CI) in association with the Chair of the DMEC. The project team should provide the DMEC with a comprehensive report, the contents of which need to be agreed in advance by the Chair of the DMEC.

Trial Team

This will comprise all co-applicants, members of the NCTU and Principal Investigators (PI) at each site. The Trial Team will be responsible for monitoring the progress of the study, addressing key issues that may arise and reporting to the funder. Meetings will take place three times a year, a month before the TSC meetings, or more frequently if required.

Trial Management Group

A core team will form the Trial Management Group (TMG) to ensure all practical aspects of the trial are progressing well and to identify potential issues as early as possible. They will meet on a monthly basis (or more frequently, if necessary) in person or by telephone conference. Email discussion will also take place when appropriate. Wider study team members, including local PIs (via video conference) will attend meetings where relevant to the phase of the study.

Young People's Advisory Group

A Young People's Advisory Group (YPAG) will be established with up to 18 young people aged 13-17 with lived experience of depression. The young people will be recruited from Hertfordshire, Norfolk and Suffolk and Bedfordshire. The group will meet three times a year, shortly before the main READY TSC, so that the views of the young people are incorporated into the key decisions. The YPAG will nominate two members to represent the group at the main READY TSC. The YPAG will be run in consultation with the young people themselves and aligned with examples of good practice of involving young people in research from NIHR INVOLVE and the National Young People's Mental Health Advisory Group. We will follow national guidance regarding role descriptions, length of group membership, safeguarding, rewards, expenses and recognition, and methods to evaluate the extent and impact of the group.

Stakeholder Forum

A Stakeholder forum with representation from Mental Health Trusts, Active Partnerships, Tier 2 Mental Health Services, Commissioners, General Practitioners (GP), Public Health Teams, NHS England, NHS Improvement and voluntary organisations will be held every six months, providing a way for the study team to communicate with the wider community, to follow policy development, to receive input into the design and delivery of the trials, and to support the dissemination programme. This Forum will have input from PPI, including PIRg and YPAG.

The study team, and the TSC/DMEC will receive reports from the YPAG (see PPI strategy) and from the Stakeholder Forum.

Clinical Trials Unit (CTU)

Norwich CTU will provide operational advice, Quality Assurance, and lead the Data Management including design, delivery and management of the trial database, Statistics and Health Economics functions in collaboration with the Clinical Trials Support Network (CTSN) at the University of Hertfordshire.

Background and rationale

Depression in adolescents

Existing research demonstrates that depression among adolescents is highly prevalent worldwide and that rates have increased significantly since the 1980s [1-3]. The risk of depression rises sharply as children transition into adolescence, with prevalence estimates of depression reported to be between 4-11% in mid-to-late adolescence and up to 20% by late adolescence [3-5], although prevalence estimates vary widely across studies and countries [4].

A significant noted trend is the rise in prevalence of depression among adolescent females compared to males, estimated at 2:1 [1-4, 6-10]. In childhood no differences are observed, but by 13-15 years, more girls are diagnosed as depressed compared to boys [11]. The reasons for this trend are not fully understood but may be related to hormonal changes during puberty, or the tendency for greater internalization of emotion in girls [4]. These findings are supported by a recent large-scale survey of 5,335 school-aged children in England (aged 11-15) which found poorer emotional health and wellbeing among adolescent girls compared to boys [12, 13].

Collishaw and colleagues [1] compared emotional problems in English 16-17 year olds between 1986 and 2006 and found twice as many young people reported frequent feelings of depression or anxiety in 2006 compared to 1986, especially girls. Also of relevance is that Lesbian, Gay, Bisexual and Transgender

young people report experiencing depression and anxiety, suicidality and self-harm at considerably higher rates than heterosexual young people of a similar age, thought to be due to factors such as homophobic, biphobic and transphobic bullying at school and perceived stigma [14, 15]. Research in the United Kingdom (UK) and other high-income countries suggests that depression is more prevalent amongst people from Black and Asian Minority Ethnic (BAME) backgrounds [16, 17]. This likely reflects a complex interplay of factors such as social disadvantage, acculturative stress, and discrimination [17, 18].

Recent research suggests that adolescents who seek help do benefit from contact with mental health services. The ROOTS longitudinal cohort study conducted in the UK [7] found that contact with mental health services by 14 year olds with depression reduced the likelihood of depression by age 17 years. This is particularly important as it is known that many young people with depression do not access mental health services, estimated at 34-56% internationally [7] , or delay seeking help, increasing the duration or risk of recurrence episodes [7]. There are also concerns regarding the use of antidepressant drugs for adolescents younger than 18 years, with a recent systematic review and meta-analysis suggesting that antidepressant use among children and adolescents poses an increased risk for suicidal thoughts and aggressive behaviour [19]. There is also a lack of strong evidence regarding the effectiveness of psychological treatments, such as Cognitive Behavioural Therapy (CBT) and Interpersonal Psychotherapy (IPT) [4]. This suggests the need for alternative approaches such as promoting changes in behaviour and health behaviours such as exercise.

Exercise, high intensity training, and depression

There are several mechanisms that have been proposed to explain the many ways by which physical activity may be beneficial in the management of depression [20]. Some of these might be via social mechanisms; physical activity participation can provide a diversion from depressive thoughts, opportunities to learn new skills, and increased socialisation [21]. In addition, there may be physiological mechanisms; physical activity is associated with promoting the release of endorphins and other neurotransmitters which can improve mood [22]. Further, inflammation has been identified as a potential contributor to the development of depression [23], suggesting that anti-inflammatory strategies, such as regular physical exercise [24] may be effective at preventing and managing depressive symptoms. However, the optimal intensity of exercise required has not been established and this information is critical when determining prescription.

Moderate levels of exercise have been shown to increase myokines which could have a positive impact on inflammation [25] and hence depression. In recent years it has come to light that performing very short bursts of high intensity exercise (30 seconds) followed by 30 seconds rest repeated for four minutes has produced increased fat oxidation and increased maximal oxygen uptake [26]. Furthermore, research has suggested that high intensity interval training (HIIT) can promote anti-inflammatory effects during recovery [27], and therefore could be beneficial for diseases with an inflammatory response [28, 29]. There remains considerable uncertainty about the extent to which exercise intensity is related to benefit for depression.

Exercise for adolescents with depression

There is growing evidence that exercise may be an effective intervention to reduce depressive symptoms in adults [30-33]. A recent meta-analysis of exercise as a treatment for depression for adults, found a large significant effect on depression, with a larger effects for outpatients, in samples without other clinical co-morbidities and when exercise was supervised [32]. For adolescents with depression the evidence base is scarce and evidence quality is poor.

A Cochrane review in 2006 [34] and subsequent systematic reviews in 2013, 2016 and 2018 [35-37], respectively) examined the effects of exercise interventions in reducing depression and anxiety in children and adolescents. Larun et.al. [34], and Brown et.al. [35] found a small effect in favour of exercise. Carter and colleagues [36] found a moderate effect on depressive symptoms in clinical samples. Bailey et.al. [37] also reported that exercise was an acceptable and feasible intervention for this target group, with low dropout. However, the low quality of the studies reviewed, the small number of studies included, small sample sizes, and a diversity of participants, interventions and methods of measurement limit the ability to draw conclusions. A recent pragmatic small scale RCT [38] conducted in the UK reported no effect on depressive symptoms at post-intervention, but a significant effect at six months in favour of the intervention, suggesting a delayed response. The qualitative component of the study [39] reported that many of the young people found the exercise motivating and enjoyable and experienced low mood and disappointment at the end of the programme. The authors concluded that large, well reported and robust trials conducted with help-seeking young people in real-world treatment settings are required.

What is the problem and why now?

Adolescence is a significant risk period for the development of depression, associated with wide ranging long-term detrimental impacts on young people's wellbeing, mental health, social, and educational outcomes [2, 40]. Adolescents with depression are a group currently underrepresented in research, underserved by child and adolescent mental health services and at high risk of continued mental health problems into adulthood. There is an urgent need to offer feasible, acceptable and cost-effective treatment options for this neglected group of young people, given the limitations and potential risks of pharmacotherapy treatment and long waiting times for psychological support. There is growing evidence that exercise is a helpful treatment for depression in young people [37, 39] but existing studies are generally small and poor quality and there remains a lack of strong evidence of cost-effectiveness. Our proposed research is clearly needed now, learning from previous research but moving forward with a definitive large-scale trial, with a clinical sample and conducted under 'real world' conditions.

Adding to the body of knowledge

Current NHS policy and practice regarding exercise for the treatment of clinical depression among adolescents is guidance-based rather than the provision of a structured and supervised exercise intervention. NICE clinical guidance [41] recommends that adolescents with depression should be offered advice on the benefits of regular exercise and encouraged to follow a structured and supervised exercise programme of up to three sessions a week, 45-60 minutes, for 10-12 weeks. However, this guidance is based on weak evidence (level IV) lacking details on intensity due to a lack of high-quality studies in this area. This study is to ascertain the feasibility of a large, adequately powered, high quality RCT with a large clinical sample of help-seeking adolescents with depression.

We expect to add valuable knowledge regarding the clinical and cost-effectiveness of an exercise intervention and its 'real world' application in the NHS and other services, along with a comparison between low intensity and high intensity exercise. We expect to provide essential evidence for the young people who might benefit, NHS policy makers, commissioners and clinicians, who are seeking evidence-based and cost-effective interventions for this specific group of young people, to offer as routine NHS care. This objective is aligned with current mental health policy to expand access to innovative and effective interventions and provide new workforce solutions [8, 10]. Our research will also add important knowledge regarding successful partnership working across the NHS and local community organisations, such as Active Partnerships, in areas with diverse populations and deprivation, to improve mental health support for children and young people [9, 42].

In summary, the existing evidence suggests that exercise is a promising and acceptable intervention for adolescents with depression. There is clear need for high quality trials in this area, with larger clinical samples, to effectively inform the implementation of exercise programmes to reduce depressive symptoms in adolescents, and to assess the influence of exercise intensity.

Aims and objectives

The aim of this feasibility study is to ascertain whether a full-scale definitive study is feasible. The objectives are to:

1. Finalise development of the intervention and control, including the Education Component (with Behaviour Change Techniques) and the intervention manual for:
   i. A high intensity exercise intervention, and
   ii. A low intensity exercise intervention with matched energy expenditure, and
   iii. An active control group of social (non-exercise) based activities

2. Finalise development of intervention training programmes for staff

3. Examine the feasibility of delivering the intervention across 3 sites (Hertfordshire, Norfolk and Bedfordshire):
   i. Explore adherence to the intervention protocol by exercise professionals, including contamination in delivery between exercise arms.
   ii. Examine the feasibility of delivering trial interventions in community settings by the exercise providers in different areas

4. Establish the potential adherence and engagement to the intervention by young people:
   i. Examine the acceptability of the exercise interventions
   ii. Adherence to the intervention, and maintenance of exercise

5. Establish potential reach and representativeness
   i. Examine demographic patterns (e.g. religion, ethnicity, gender, socio-economic status) in participants and non-participants to inform the recruitment strategy for the main trial

6. Examine the feasibility of delivering a randomised trial at scale:
   i. Estimate referrals, recruitment and retention rates
   ii. Compare referral pathways
   iii. Estimate adherence rates to exercise
   iv. Determine the acceptability of the interventions
   v. Explore the feasibility of collecting outcome and resource use data
   vi. Evaluate the safety of the trial interventions
   vii. Confirm the number of required sites and sample size for the main RCT

The findings will be used to refine the intervention and study delivery for the full-scale trial.

The TMG will report to the TSC and DMEC protocol changes, adverse events, recruitment, adherence to the intervention and the feasibility of proceeding with main trial. Trial progress will also be routinely reported to the NETSCC, and progress to the next phase commenced once confirmation is received.

Methods

Design

The READY feasibility trial is a multi-site, three arm, three site, cluster RCT. The arms are High intensity exercise, Low intensity exercise and Active social control. Eighty-one participants will be recruited over twelve months. Each participant will be offered 24 intervention sessions (two a week, for 12 weeks) and are followed up for six months (at 14 and 26 weeks from randomisation) following completion of the intervention.

This feasibility trial will include three sites, who will provide data on referrals and eligibility, establish the feasibility of recruitment, and delivery of the interventions to 81 young people. The trial will include an intervention protocol, adapted if needed, and reported according to the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) and template for intervention description and replication (TIDieR) checklists [43].

A process evaluation will be conducted. In this feasibility study, triangulation of the analysis (see Data Analysis section) of the intervention logs, focus groups and case report forms will be used to describe, and examine delivery of all three arms and adherence to the training and delivery of all three arms in order to refine the intervention and study delivery for the full-scale trial. In addition, semi-structured interviews with research staff, young people and parents or caregivers will be conducted during the recruitment period to investigate barriers to recruitment.

To inform the Economic evaluation in the future trial we will examine the feasibility of collecting and analysing the costs and effects of the exercise interventions, both in terms of reduced depression, and changes in health-related quality of life (HRQoL).

Setting

The READY feasibility trial is a multi-site study taking place in Hertfordshire, Norfolk and Bedfordshire. Young people will be recruited from CAMHS; (Tiers 2 and 3), other Tier 2 services and GP practices (Tier 1). Tier 2 services may be provided by NHS Trusts, but in some areas, they are provided by the third sector (e.g. in Norfolk and Waveney, Point 1 provide these services).

The intervention will be delivered by Level 3 or 4 Registered Exercise Professionals (REPs) employed by Active Partnerships.

The NIHR Clinical Research Network (CRN) Eastern will be the lead CRN and will help identify study sites and sources of referrals (PIC sites) in preparation for the full trial. The team has links with the GPs & Mental Health Commissioning lead, and the Diverse Cultures Team, Bedford, which has a high BAME population.

Site/Investigator Eligibility Criteria

To participate in the READY trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the READY Trial Management Group (TMG) and that are defined below.

Eligibility criteria:

- A named clinician is willing and appropriate to take Principal Investigator responsibility
- Suitably trained staff are available to recruit participants and enter data
- Have established links with exercise providers that can deliver the intervention locally, or willing to work with exercise providers to deliver the intervention locally

- Have in place a local referral pathway (e.g. Crisis team) for participants, or parents/carers of participants, to access should the mental health status of the young person deteriorate during the trial.

Trial sites meeting eligibility criteria will be issued with the READY Site File and a pack of documentation needed by the Research and Development Department (R&D) of their Trust to enable the Trust to provide confirmation of capacity and capability to undertake the study.

Three sites will participate in the feasibility study. Two sites were pre-selected on the basis of co-applicant commitment to the study:

- Hertfordshire (Hertfordshire Partnership University NHS Foundation Trust and Hertfordshire Community Trust)
- Norfolk and Waveney (Norfolk & Suffolk NHS Foundation Trust),

The third site will be Bedfordshire (East London NHS Foundation Trust).

Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing to sign an investigator statement to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, familiarity with the intervention, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related duties.

Resourcing at site

The investigator(s) should be able to demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period (e.g., the investigator(s) regularly treat(s) the target population). They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to conduct the trial properly and safely.

Sites will be expected to complete a delegation of responsibilities log and provide staff contact details.

The site should have sufficient data management resources to allow prompt data return to NCTU.

Participant Identification

Participants will be identified by CAMHS (Tiers 2 and 3), other Tier 2 services and local groups. Self-referrals will also be permitted. In addition, a selection of GP practices (tier 1) in these areas for the participating sites will be recruited as participant identification centres (PIC sites) to identify and refer potential participants.

Site Approval and Activation

On receipt of the signed investigator statement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The trial manager or delegate will notify the PI in writing of the plans for site initiation. Sites will not be permitted to recruit any patients until a letter of activation has been issued. The Trial Manager or delegate will be responsible for issuing this after approval to recruit process has been completed.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and Health Research Authority (HRA), and which was given favourable opinion by the Research Ethics Committee (REC). The PI or delegate must document and explain any deviation from the approved protocol and communicate this to the TM.

A list of active sites may be obtained from the TM.

Sampling: Feasibility of recruitment

The target sample sizes for the feasibility study is N=81, with each study site (typically a county) expected to recruit approximately seven young people per month. The recruitment model assumes that approximately 10% of young people eligible from list screening will be randomised to the trial. The main organisation at each site is likely to be the CAMHS service (with responsibility to ensure clinical safety), with independent Tier 2 providing referrals, and GP services acting as participant identification centres (PIC).

Surveys of services indicate that typically 186 young people per year are identified as eligible in a CAMHS Tier 3 service (64% of young people referred), and 1408 young people per year from a Tier 2 service (80% of young people referred). Screening of GP practices lists show on average 548 eligible young people (65% of young people seeking support in the past year). Assuming that 10% of eligible young people across these services (N=1594) identified on record searches will be randomised, the survey indicates that typically a study site should be able to recruit 159 young people per year from CAMHS (Tier 2 and 3). When supplemented with research active GP practices the recruitment potential should be in excess of 200 young people per year in each site. These assumptions will be tested during the feasibility phase.

Participants

A minimum of 81 young people will be recruited across three sites (an average of 27 per site). The study population will be young people ages 13 to 17 who have sought help for feeling low, or depression in either a primary or secondary care setting. The parents or carers of recruited young people will also be recruited to the study to provide information relating to the participants' mental health and to capture information about caregiver burden. Given the design of the group therapy intervention, it is possible that recruitment beyond 27 per site may occur.

The study will identify young people, presenting to a health care setting, who have mild to moderate symptoms of depression (CDI 2 score >=17 and <=36). To increase generalisability young people who are currently being treated for depression (drug or psychological therapy) or have a comorbid physical or mental health condition (e.g. chronic pain) will be included, provided that they meet the criteria for inclusion.

Parent and carer involvement will be encouraged through engagement in the study assessments, and by providing an information pack about the intervention and the study. The content of the pack will also provide standard information about depression in young people, crisis support information, and the potential value of exercise in reducing depression. The pack will support the parents to support the young person during and after the intervention. The parents will be asked to provide data at baseline and follow-up.

Inclusion/Exclusion criteria

In order to be as inclusive as possible, any young person meeting the inclusion criteria for low mood or depression should be considered for the study. Low mood or depression does not need to be the

primary diagnosis and comorbid conditions that do not preclude exercise should not be a barrier to inclusion.

Inclusion criteria:

- Help-seeking adolescents aged 13-17 years with a CDI 2 score between 17 and 36, inclusive (mild to moderate symptoms).
- Current treatment with antidepressants or other drug, or psychological therapy is allowed
- Young person understands their role in the trial and is able to complete trial activities
- Young person consent to participate, with consent from parent/carer for under 16s and consent of parent/carer to provide data
- Parent/carer/guardian also taking part in the study
- Young person and parent/carer is able to complete the questionnaires in English
- Young person able to attend the intervention session

Exclusion criteria:

- Considered unsuitable by the clinician screening for eligibility
- Current treatment, or co-morbid conditions present contraindications to engaging in RCT or exercise
- Active psychosis, significant substance abuse, self-harm, or suicidal ideation presenting significant risk (assessed as part of the DAWBA)

Procedure

The Gantt chart shows the timeline of this study and the study flowchart can be seen below (Figure 1), along with the study schedule (Table 1). The GANTT chart is available to view on the TMF. The Case Report Form (CRF) has been designed to reflect and support the flow of the study, and to record details of actions taken and dates.

The research team will use File Notes to record any issues and these will be discussed with the TMG. If appropriate, issues will be reported to the TSC.

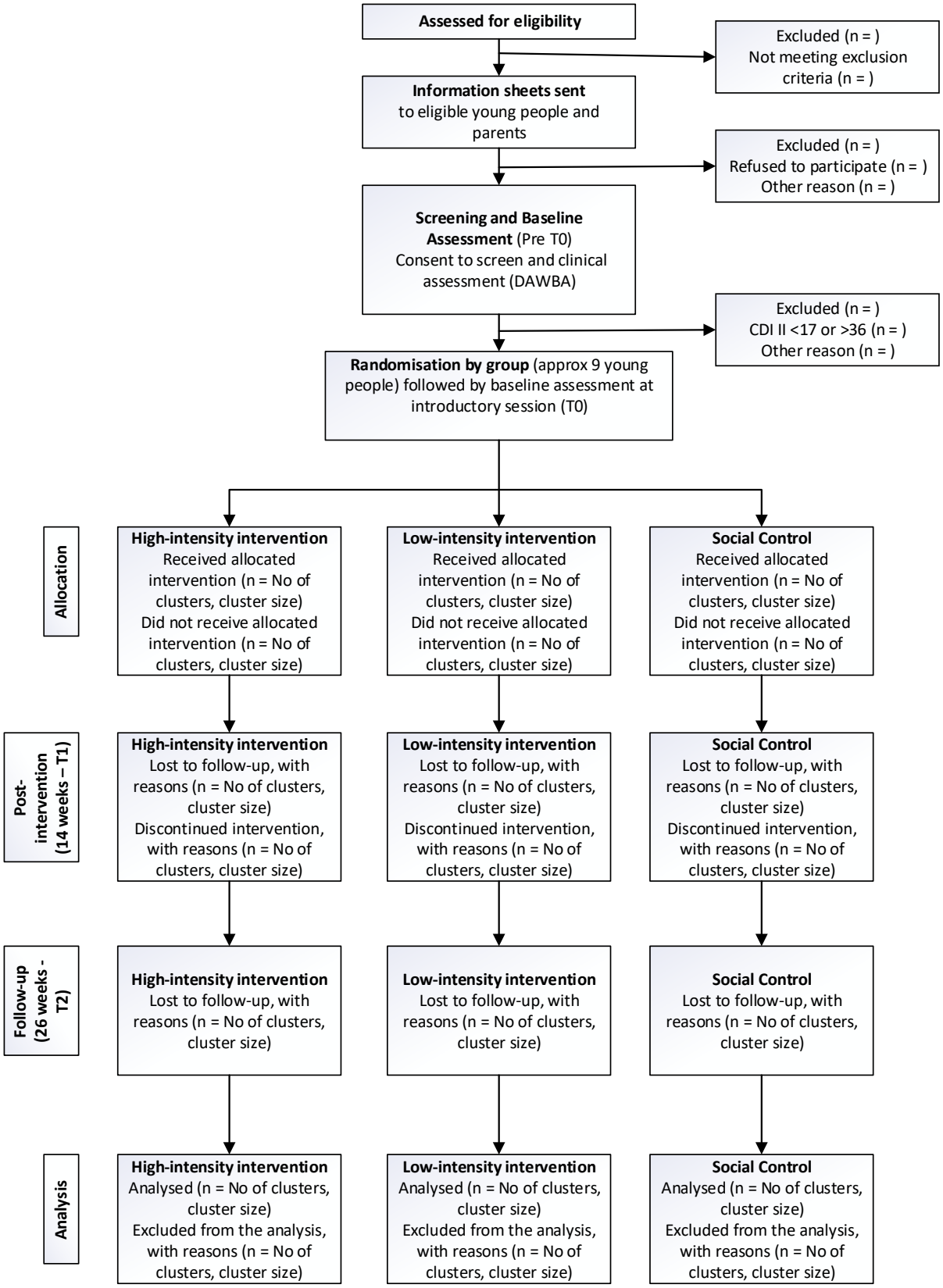


Figure 1. Feasibility Study Flowchart

Table 1. Study schedule

	STUDY PERIOD						
	Screening	Randomisation	Post-randomisation				Post randomisation follow-up
TIMEPOINT	**Pre-T0**	**Pre-T0**	**T0**	**T0-T1**	**T1 +14 wks**	**T2 +26 wks**	
ENROLMENT:							
Eligibility screen	X						
Referral to research team	X						
Informed consent	X						
Randomisation		X					
INTERVENTIONS				X			
ASSESSMENTS:							
CDI-2	X		X		X	X	
Demographic information	X						
DAWBA (includes SDQ) CYP completed	X						
DAWBA (includes SDQ) Carer completed	X						
PAR-Q	X						
PANAS			X		X	X	
Self-efficacy scale			X		X	X	
Social Support Scale			X		X	X	
Caregiver burden			X		X	X	
Adherence				X			
Peak and average HR				X			
Ratings of Perceived Exertion				X			
Measured physical activity			X		X	X	
Y-PAQ			X		X	X	
COM-B measures			X		X	X	
EQ-5D-5L			X		X	X	
CSRI			X		X	X	
CHU-9D			X		X	X	
Focus Groups							X
ADVERSE EVENT MONITORING			X	X	X	X	X

Note: FU = Follow-up. T0 = Baseline, T1 = First FU, T2 = Second FU. CDI-2 = Clinical Depression Inventory – 2. DAWBA = Development and Wellbeing Assessment. SDQ = Strengths and Difficulties Questionnaire.

CYP = Child or Young Person. PAR-Q = Physical Activity Readiness Questionnaire. PANAS = Positive and Negative Affect Schedule. Y-PAQ = Youth Physical Activity Questionnaire. CSRI = Client Service Receipt Inventory. CHU-9D = Child Health Utility 9D

Trial set-up

Trial set-up will involve obtaining approval from the HRA, which comprises review by a NHS REC, and assessment of regulatory compliance, registration on the CRN portfolio, clinical trials registration on ISRCTN registry and database set-up. The ethics committee at the University of Hertfordshire will also be informed of the study and sponsorship will formally be applied for. Study personnel will be recruited: Trial manager and Research Assistant at UH and the Mental Health Support Worker (MHSW) at each site. Liaison with the Active Partnerships will take place to identify sites and the REPs who will deliver the intervention. Good Clinical Practice training will be undertaken by those the CIs deem requires it for their role in the study. The Trial Steering Group, Data Monitoring committee, Trial Management Group, Youth Council Reference Group and Stakeholder Forum will be established, and meeting dates will be agreed. A study website will be developed and launched.

Recruitment

Participant identification and screening of referrals

In Tier 2 and Tier 3 services, the CAMHS Single Point of Access (SPA) in each setting will review incoming referrals to identify those who might be eligible to join the study (i.e. are the right age, have reported low mood/depression and with no obvious reason why they cannot participate). Within each service, a member of the clinical team will review their current caseload/waiting lists and incoming referrals to identify appropriate young people currently being treated or being referred into CAMHS.

Young people will be informed about the study and asked whether they would be interested in taking part. Only those who are located within easy travelling distance from the location where the intervention will be delivered will be approached about the study (in the case of face-to-face delivery). Those that are interested will be asked for consent for their details to be passed to the study team. A member of the research team (throughout this refers to either a research nurse, a Clinical Studies Officer, A Clinical Research Practitioner, an assistant psychologist, a Mental Health Support Worker, a Research Assistant or a member of the central study team, as appropriate) will contact the young person, send the participant information sheet (PIS), if not already provided, and arrange an appointment at a convenient date/time to receive informed consent and to conduct the screening assessments.

In primary care settings young people identified as potentially eligible (i.e. are the right age, have reported low mood/depression and with no obvious reason why they cannot participate) from current GP lists will be sent information about the study and invited to contact the study team. Initial suitability for the study will be assessed via a phone call between the potential participant, and parent/carers/ guardians where appropriate, and a member of the research team.

Some young people might self-refer to the study. They may find out about the study from their peers, from the study website, via social media, from the Sports Partnerships, from schools pastoral care or counselling services, local community centres or from promotional materials (poster/leaflet) displayed in GP surgeries, schools and community centres. They will be directed to the R&D department at their local NHS Trust. A member of the research team will discuss the study with them and check for their eligibility/suitability to take part in the study.

Screening

Informed Consent

Feasibility Study

Consent will be managed sensitively given the age of the young people. Participants will have been given sufficient time to read the information provided to them in the PIS. They will be given the opportunity to ask questions they might have. If they are willing to continue, then they will be asked to provide consent/assent. The parents or carers will be consented to provide study assessment about the young person in their care (this is an inclusion criteria). Young people aged 16 or older will provide consent, and those under 16 will also be asked to provide assent to participate but will also require consent to be provided by their parent or carer. In some cases the role of the parent may be taken by a legal guardian (foster carer, or Social Services) and in these cases relevant consent, and engagement by carers (sometimes not the legal guardian) will be facilitated.

Recruitment Evaluation

If a potential participant declines to take part in the study after having a conversation with a researcher, they will be asked if they would be willing to provide verbal consent for another researcher to contact them about speaking with a member of the process evaluation team about their experience.

The researcher will record the contact details of participants who agree to be contacted to discuss their experience. Participants who agree will be sent further information in the form of a PIS about taking part in an interview. Informed consent will be sought.

Interviews will be conducted by a member of the process evaluation team and recorded for transcription by a member of the research team at a later date.

Recordings will not be used or listened to by anybody outside of the research team. All members of the research team and process evaluation team will have the appropriate research passports and letters of access for each study site in place in order to perform these activities.

Focus Groups

Informed consent will be gained from all participants and staff agreeing to take part in the focus groups at the end of the intervention. All participants and staff being interviewed will be provided with a PIS. A researcher will briefly introduce the study and will allow participants the opportunity to ask questions. A consent form will be provided for participants to sign.

Screening measures

- **Child Depression Inventory** 2nd edition (CDI-2) [44]) Measures depressive symptoms in youth aged 7-17 years. It is a self-report measure and takes 5-15 minutes to complete.
    - Young people with a score <17 or >36 (moderate to severe depression likely) will be referred back to the clinical practice that referred them for further assessment and treatment, according to local site protocol. If the young person self-referred, then they will be referred to their GP.
    - Those young people with a CDI score >=17 and =<36 will be asked to complete the DAWBA, and consent will be sought for parents (or carer) versions of the DAWBA to be

completed.

- **Development and Wellbeing Assessment** (DAWBA: [45]). Online assessment tool used to identify potential diagnoses and assess risk which includes the Strengths and Difficulties Questionnaire (SDQ: [46]). The self-report version for young people takes up to 30 minutes to complete. The parent/carer version takes up to 50 minutes.

- **Physical Activity Readiness Questionnaire** (PAR-Q) short version [47]. This is a self-report that measures the young person's readiness to take part in exercise. If the answer to any of the questions is "yes" we will advise them to go to their GP and check that it is okay to participate in the study.

Screening measures will be completed online using a computer or any mobile device. All research staff involved in administering these measures will receive training from members of the study team experienced in using these measures.

The member of the research team administering the screening measures will ask the young person and their parent/carer about any current treatment with antidepressants or other drug, or psychological therapy that the young person is receiving, and this will be used to assess whether any current treatment, or co-morbid conditions present contraindications to engaging in RCT or exercise.

Following the meeting with the young person the results from the screening measures will be reviewed by the PI and the member of the research team who conducted the assessment to determine the suitability of the young person to join the study. On completion of this assessment, young people who are identified as being at significant risk (from the DAWBA) will be referred back to the clinical service for further assessment and treatment, as required. If the young person self-referred, then they will be referred to their GP.

Young people will be contacted by a member of the research team and advised about their eligibility. If they are not eligible, they will be advised why, what the next steps are (e.g. to be referred back to their referring service or to wait to be allocated to a group) and signposted to services, if appropriate.

Young people and parents assessed as being suitable for the study will be randomised as follows.

Allocation/Randomisation

Eligible participants who have consented to the study, will be randomised in groups of approximately nine participants, as soon as each group of nine has accrued. Each group will either be a single-sex group or will include at least two girls or two boys.

Sequence generation

The allocated treatment for a group will be generated via computer written code using stratification with random permuted blocks. Stratification will be by study site.

Full details of the allocation algorithm (including the block size) will be documented in a separate document (called Allocation System Specification for READY) stored in a shared file accessible to only the study statistician and data manager until the end of the study.

Allocation Implementation

The groups will be allocated to the intervention by a process embedded in the web-based data Management system. The randomisation code will be saved in the study database for later decoding. When a group is randomised an email will be sent to the PI, the Trial Manager, the MHSW and the REP for them to set up the appropriate intervention.

Blinding

Allocation blinding is not possible, but outcome assessment will be blinded where possible.

Baseline

The young person will be contacted by a member of the research team informing them that they are eligible for the study and the intervention to which they have been randomised. They will be given details of where and when the first session will be, along with details of all planned sessions by a member of the study team.

The first session will be an introductory session (T0) where the young person will have an opportunity to meet the other members of the group, the REP and MHSW. They will learn about the format of the sessions and additional requirements of the trial. This has been included following feedback from our consultations with young people to support and maintain engagement of the young people and their parents or carers recruited to the trial.

During this session they will be asked to keep the research team advised of any change in their health while they are in the study. They will be informed that it is important that the team are advised of anything that has happened to them that they consider to be important.

The times taken to complete the questionnaires will be recorded to inform the design of the main study about how much burden the forms represent.
They will be asked to complete the following baseline measures at the beginning of the session:

Completed by the Young Person:

- Child Depression Inventory 2nd edition (CDI-2: [44]) Measures depressive symptoms in youth aged 7-17 years. It takes 5-15 minutes to complete.
- Positive and Negative Affect Schedule (PANAS [48]). Self-report questionnaire with two sub-scales for positive and negative affect. Takes about five minutes to complete.
- New General Self-Efficacy scale. Eight-item measure to assess how much people believe they can achieve their goals. Being used to address personal agency to engage in exercise [49]
- Multidimensional scale of perceived Social Support (MSPSS[50]) – Twelve-item measure designed to measure perceptions of support from family, friends and a significant other. It takes 5-10 minutes.
- A six-item measure will ask participants how much they agree that they have the Capability (Physical and Psychological), Opportunity (Social and Physical), and Motivation (Reflective and Automatic) to be regularly active (COM-B measure). This measure will take less than five minutes to complete and the validation paper is in the process of being published.
- EQ-5D-5L – A measure of Health-Related Quality of Life (HRQoL). Uses both descriptive scales and a visual scale (EuroQol Visual Analogue System (EQ-VAS)).
- Modified client service receipt inventory (CSRI)- completed with the MHSW. If the young person is unable to complete this measure, then the parent/carer will be asked to provide missing information.
- Ratings of perceived exertion [51] – Measures perceived exertion and will be administered at each intervention

- Child Health Utility 9D (CHU-9D: REF [52]) – A health related quality of life questionnaire which will take approximately 5 minutes to complete. There are nine multiple-choice questions, each with a choice of five answers.
- Youth Physical Activity Questionnaire (Y-PAQ: [53]). Self-report questionnaire assessing physical activity over the past 7 days.

Completed by the Carer:

- Burden Scale for Family Caregivers – short form (BSFC-s) [54]. Ten-item scale to measure perceived burden on families.
- Any information that the young person was unable to provide on the modified CSRI (see above).

Physical Activity

- Following the baseline assessment, the young people (in all groups) will be provided with an accelerometer and shown how to use it and asked to wear the accelerometer for 7 days before the first intervention session. The young person will be allowed to remove the accelerometer for washing if preferred but encouraged to keep the accelerometer on while asleep. (This will be repeated at week 12 and 26.)

The MHSW will be on hand to help the young person with any questions they find difficult or to provide support if they become distressed as a result of completing them.

If any young person or parent/carer is unable to attend this introductory session, arrangements will be made for them to be provided with the accelerometer and to complete the baseline outcome measures separately.

Intervention Measures

After the baseline session there will be 24 intervention sessions, conducted twice a week for 12 weeks. The following will be recorded at each intervention session:

Physical activity:

- Peak & average heart rate during the intervention sessions (weeks 4 and 8 (±1 week), face-to-face meetings only)
- Ratings of perceived exertion

Attendance Rates:

- Record of attendance at each group (including recording if they do not attend the whole session)

Trial intervention safety

- Recorded adverse events, as defined in the next section

Interventions

All three interventions will be delivered in supervised small groups of 9-10, at local community venues or online should circumstances dictate, twice a week over 12 weeks by REPs with additional training in mental health, in conjunction with MHSWs.

The REPs and MHSWs will attend an initial two-day workshop, with one day focused on running the exercise sessions and research skills related to outcome assessment and data management, and another day will focus on encouraging attendance and longer-term behaviour change. This will cover the behaviour change session content and communication skills using motivational interviewing [55], and how to deliver the Behaviour Change Techniques (BCT) with an emphasis on expressing empathy and being client-focused [56]. This training will highlight the need to Engage the patient in the consultation process, Resist telling them what to do, allowing Focus on what is desired and achievable, to Understand the patient's perspective, Evoke a sense of empowerment, ensure that the client feels Supported and has a Plan going forward [57]. Core communication skills to support effective group discussions [58, 59] such as RULE (Resist the righting reflex; Understand your client's motivation; Listen to your client; Empower your client) and OARS (Open-ended questions, Affirmations, Reflective listening, Summaries) will be covered, and linked to the delivery of the BCTs.

A further training day, two weeks later, will then focus on consolidating the exercise, delivery, behaviour change, and research skills. Throughout the 5-month delivery period the REPs and MHSWs will have four further half day workshops to reflect on challenging and successful group discussions, and to get expert and peer review of their intervention delivery. The training sessions will be led by an expert in behaviour change and health psychology with 15 years of training experience (AC), an exercise physiologist (LB), and a research fellow in physical activity and behaviour change (NH).

This model of delivery is based on feedback from young people, the team's experience and the importance of adherence [60].

BCTs will be derived from the Behaviour Change Wheel, COM-B model [61] and the Theoretical Domains Framework (TDF; [62] used as a theoretical base for the 'Healthy Living' component of the intervention [61, 63, 64]. Previous trials have offered sessions twice a week for shorter duration [38] and three times a week for 12 weeks [65, 66], reporting an initial high adherence which declined over time [65]. The full intervention content will be informed by a range of important stakeholders and detailed in a comprehensive intervention manual, which will be finalised before recruitment starts.

For the first 15 minutes of each of the sessions, there will be a Healthy Living session focusing on promoting and maintaining behaviour change. There are three main objectives of the Healthy Living sessions:

- to help ensure the young people attend the sessions and engage with the intervention.
- to facilitate the young people to participate in physical activity outside of the intervention,
- to encourage the sustainability of physical activity engagement after the intervention is completed.

To ensure equivalence, study staff will deliver the Healthy Living sessions in all three study arms.

Behaviour change, and maintaining engagement

The Healthy Living sessions are focused on encouraging engagement of the young people in the intervention, and on promoting and maintaining behaviour change. These sessions will include key Behaviour Change Techniques (BCTs), delivered through Motivational Interviewing, to promote engagement and enable young people to drive their own goals, education and behaviour change. The BCTs will target theoretical drivers from the COM-B and TDF to target barriers and facilitators in Capability, Opportunity, and Motivation. Barriers, highlighted by our consultations with young people, include a lack of 'head space' or stamina for exercise (Psychological and Physical Capability), lack of social support (Social Opportunity), negative beliefs about exercise (Reflective motivation), and emotions that lead to avoidance (Automatic Motivation). Potential facilitators were suitable

environments to increase access and enjoyment (Physical Opportunity), manageable sized groups (6-10 young people), peer support (Social Opportunity), setting goals and increasing positive expectations about exercise (Reflective Motivation).

Motivational interviewing (MI) will be used to deliver BCTs that will target these barriers and facilitators to enhance intrinsic motivation [58, 67], and also address potential depression-related barriers using aspects of behavioural activation, such as activity scheduling and reducing avoidance. The final content of the Healthy Living sessions will be based on a combination of consultations with a range of young people, exercise professionals, expert stakeholders and project team members (at the start of the study).

All young people in the study will continue to receive usual care (healthy lifestyle advice, encouraging physical activity, psychological therapy and, or drug therapy as needed), from the referring NHS service.

The interventions are as follows.

1. **High intensity physical exercise** of alternating training sessions [68, 69] (e.g. basketball, football, circuit training to music, boxing drills) beginning with a 10-min warm-up, culminating with a 5-min whole body cool down. Young people will perform four repetitions of 45-seconds of maximal effort exercise (>90% predicted maximal heart rate) with 90-seconds rest in between each repetition (approximately 10 min) which will increase by 1 repetition every two weeks [70] building to 12 repetitions. Heart rate monitors will be used at weeks 4 and 8 (±1 week) during face-to-face meetings to tailor each person's maximum intensity [71]. These exercises are based on research by Weston et al. [68] who developed the protocol from qualitative data collected at focus groups from adolescent school children. It incorporates activities which will appeal to both males and females.

2. **Low intensity physical exercise** of alternating training sessions [72] (e.g. walking sport such as football and netball). These low intensity activities elicit a heart rate between 40-50% maximal effort based on the activity compendium [73]. The sessions will follow the same warm up and cool down as the high intensity, but the overall exercise session will be longer (to energy match to high intensity) and will start at 32 minutes of exercise (increasing by 6 minutes every other week).

The energy levels have been previously matched.

3. **The active control** will receive the same Healthy Living session in addition to 45 minutes of social non-exercise activities twice a week for 12 weeks. These will include activities such as board and computer-based games, and group discussions, with the exact activities agreed upon by the group. The purpose of these control activities is to provide a comparative length of time and social context, which does not involve exercise, to control for any potential social benefits for depression of the two exercise conditions. The Healthy Living session remains almost identical to avoid introducing variables other than supervised exercise sessions into the study design. Young people in all three arms will be encouraged to engage in appropriate intensity activities between sessions, and after the intervention ends to maintain their physical activity levels.

Intervention Delivery

Active Partnerships provide a nationwide infrastructure that is tasked to support the promotion and delivery of exercise interventions in public health, with methods developed to support the engagement of hard to reach and disadvantaged populations.

The Active Partnerships will signpost to appropriate REPs, who in partnership with a MHSW from the main mental health NHS Trust in each area, will deliver the planned interventions in this study. A REP engaged by the Active Partnerships and a MHSW engaged by the CAMHS service will work together as a

team to deliver the group sessions. This provides a direct clinical link to the mental health service should the young people in the study require additional support (e.g. in response to a mental health crisis). Sessions will run during school terms, as far as possible, at accessible venues and convenient times or online should circumstances dictate.

End of the Intervention.

The referring service will be informed in writing when the young person has finished the intervention, and how many sessions they attended.

Follow up Measures

To maximise engagement with the young people in the study follow-up is planned as a group session (in trial groups) either in person or remotely. Individual follow up will be available if the young person is reluctant or unable to attend the group session. Parents will be followed-up remotely using electronic platforms.

At the twenty-second intervention session, young people will again be provided with an accelerometer to wear for a week. They will be asked to return this at the final intervention session, one week later.

The first follow-up will take place during the last intervention session (T1 - 14 weeks after randomisation). The young people will be invited to a final group session 26 weeks after randomisation (T2). The date for this final session will be provided to participants at the final intervention session. An accelerometer will be sent to them two weeks beforehand and participants will be asked to wear it for one week before, and to return it at the session. The covering letter will serve as a reminder of the appointment.

Completed by the Young Person:

- Child Depression Inventory 2nd edition (CDI-2)
- Positive and Negative Affect Schedule (PANAS)
- New General Self-Efficacy scale
- Multidimensional scale of perceived Social Support (MSPSS)
- COM-B measure
- EQ-5D-5L
- Modified CSRI
- Y-PAQ
- CHU-9D

Completed by the Carer:

- Burden Scale for Family Caregivers – short form (BSFC-s)
- Any information that the young person was unable to provide on the modified CSRI

Trial intervention safety

- Recorded adverse events, as defined in the next section

Physical Activity

At each follow-up time point the young people will be sent an accelerometer, with information reminding them how to use the device, 10 days before the follow-up session. The young people will be asked to wear the accelerometer for seven days prior to attending the meeting as at baseline.

Payment

Young People will be given £10 in vouchers each time they complete study outcome measures at follow-up (i.e. up to £20 in total).

Recording/Reporting of Adverse Events

Table 2: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant which does not necessarily have a causal relationship with the trial intervention. Adverse events include: ● an exacerbation of a pre-existing illness ● an increase in the frequency or intensity of a pre-existing episodic event or condition ● a condition (regardless of whether PRESENT prior to the start of the trial) that is DETECTED after the start of the trial. (This does not include pre-existing conditions) ● continuous persistent disease or a symptom present at baseline that worsens following administration of the trial treatment Adverse events do NOT include: ● Medical or surgical procedures: the condition that leads to the procedure is the adverse event ● Pre-existing disease or a condition present before treatment that does not worsen ● Hospitalisation where no untoward or unintended response has occurred e.g. elective cosmetic surgery
Related Event (RE)	Any untoward and unintended response to a trial intervention
Serious Adverse Event (SAE) or Serious Related Event (SRE)	Any AE or RE that: ● results in death ● is life threatening* ● requires hospitalisation or prolongs existing hospitalisation** ● results in persistent or significant disability or incapacity ● is a congenital anomaly or birth defect ● or is another important medical condition***
* the term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g. a silent myocardial infarction) ** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE	

*** Medical judgement should be exercised in deciding whether an AE or RE is serious in other situations. Important AEs or REs that may not be immediately life threatening or result in death or hospitalisation but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table.

Adverse Events

Any adverse event (AE) occurring during the participation phase of the study should be reported in accordance with the READY Safety Reporting guidance, study protocol and local Trust policies. The definition of the 'participation phase' is from the point of consent to the end of that person's participation in the study (completion of the final follow-up assessment or until formal withdrawal, whichever is sooner).

Working Definition of an AE

An AE should be reported if a participant:

- Has had a change in clinical presentation of their mental health condition which requires further referral to health services, such as a GP, but has not required a hospitalisation. For instance, onset of suicidal ideation or a change in self-harming behaviour since their participation in the trial.
- Has attended/been attended by emergency services but has not been admitted to hospital. For instance, has attended Accident and Emergency (A&E) to seek treatment for non-life-threatening injuries resulting from self-harm and is discharged home within 24 hours (however, see further guidance below about when an A&E attendance should be reported as a SAE).
- Has been diagnosed by a health care professional with a condition which required non-urgent medical intervention e.g. a prescription for medication or non-urgent referral to secondary mental health services.
- Reports the onset of a new symptom, or a marked increase in the frequency or severity of an existing symptom, but which has not required a hospitalisation. This includes a report of an instance of a type of self-harm not reported at baseline, or any concerns raised by the young person themselves, a parent or professional about a worsening of emotional or behavioural difficulties.

Potential escalation of an A&E attendance from AE to SAE

When an A&E attendance by a participant is in response to a potentially life-threatening situation e.g. when a participant has attempted suicide or self-harmed using a potentially life-threatening method, it should be reported as an SAE for it to be assessed as a potential Serious Related Event (SRE). An SAE form should be submitted, and the reporting person should work with the local PI, clinical care team (and family if deemed appropriate) to ascertain and report to the CI and the clinician providing medical oversight for the study as soon as practically possible the following information:

- Is this behaviour in line with the baseline presentation of the participant?
- Has there been any change in frequency, method and intent of self-harm or suicide attempts?
- Is the patient currently receiving the READY intervention, or have they recently finished the intervention phase?
- Is there any other recent change in the person's life that may be a contributory factor for the life-threatening situation?

This information should be rapidly assessed.

Researcher responsibilities relating to safety reporting

When an adverse event occurs, the member of the study team who first becomes aware of the adverse event must assess whether or not the event is serious using the definition given in Table 2. If they are unsure of whether the event should be classified as serious, the team member should consult the local PI.

All AEs assessed as non-serious, whether expected or not, should be recorded in the participant's medical notes (if applicable) and recorded on the study database within 7 days. If it is apparent to any member of the study team that a number of AEs have been reported for one participant, they will refer this to the local PI who will review and escalate to the TM and CI, if necessary.

All SAEs should be notified to the Trial Manager within one working day and an SAE form completed. This completed and signed SAE form should be emailed to the Trial Manager (or delegated person in the absence of the Trial Manager).

The Trial Manager will review the SAE form and disseminate to the CI, PI, local R&D and the sponsor and the appointed clinician who provides clinical oversight for the trial within 72 hours of being informed. The DMEC and REC will be informed by the Trial Manager of SAEs periodically unless the CI or sponsor escalates the SAE or deems necessary.

Causality

As this is a non-CTIMP, SRE cannot be escalated to SUSAR (suspected, unexpected, serious adverse reactions). However, expectedness of the SRE will be evaluated to consider if there is at least a possible involvement of the trial procedures (including any comparators) by the investigators and sponsor. **Expectedness of AE's and SAE's are assessed by the CI or delegate by checking the reported event against the list of expected events: low mood; suicidal ideation; self-harm that *not* require attendance at a hospital emergency department/A&E; substance abuse (e.g. drinking alcohol, taking illegal drugs); distress in therapy sessions**.

If an SRE is assessed as being unexpected, the CI is responsible for the reporting it to the REC within 15 days of becoming aware of the event. It will also be reported to the DMEC.

The CI (or a clinically qualified delegate) will review all SAE reports received. The CI must assess the causality of all serious events in relation to the trial intervention using the definitions in Table 3.

An up to date log will be kept of all SAEs and SREs in the Trial Master File. These will be documented in the Annual Progress Reports to the REC.

Table 3: Causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (e.g. the event did not occur within a reasonable time after commencement of the trial intervention). There is another reasonable explanation for the event (e.g. the	Unrelated SAE

	participant's clinical condition or other concomitant treatment)	
Possibly related	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after commencement of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant treatment)	SRE
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	SRE
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SRE

If an SAE is considered to be related to the trial intervention, and the intervention is discontinued or interrupted for that participant as a result, this should be recorded in the appropriate sections of the database, including withdrawal form if they leave the study. .

The study team may become aware of AEs from a number of sources such as the young person, their parent/carer, crisis team. In particular, at each exercise and follow up session the young people will have contact with the registered exercise professional and mental health support worker. If any adverse events are observed at these times they will be recorded on the database. The MHSW will be the point of contact for the young people so may obtain information on adverse events experienced in between the exercise sessions. These will also be recorded in the adverse event report.

At the baseline visit all participants, parents and carers will be given information about accessing help locally (e.g. Crisis team) should the mental health status of the young person deteriorate.

The local PI should ensure that local guidelines for safety reporting are followed for all reportable events.

Withdrawal Criteria

In providing informed consent into the trial, participants and / or parents /carers are consenting to trial treatments, contact, randomisations, assessments, follow-ups and further data collection.

Participants may withdraw from the study (before or after intervention, and not agree to data collection) or withdraw from treatment (during intervention, but participant or carer/parent agrees to data collection)

However, participants may stop treatment early or be stopped early for any of the following reasons:

- Adverse event
- Responsible clinicians for a patient deem it necessary to withdraw a patient for appropriate medical reasons
- An inter-current illness (i.e. one that develops or occurs as a result of their primary illness) prevents further treatment

- Any change in the participant's condition that in their clinician's opinion justifies the discontinuation of treatment
- Withdrawal of consent for treatment by the participant
- Disengagement or inability to maintain contact

The participants will be explicitly made aware of their rights to withdraw from the trial and how to do this. This will be made clear to the participant within the information sheet and at the point of receiving informed consent.

It is important to note that, as participation in the trial is voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled and without giving reason. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Participants who discontinue protocol treatment / are withdrawn, for any of the above reasons, should remain in the trial for the purpose of data collected, follow up and data analysis unless explicitly stated by the participant. All data collected up to the point of withdrawal of consent will be retained in the trial dataset.

If a participant chooses to discontinue their trial treatment / are withdrawn, they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing and are still able to consent to this.

They will be encouraged and facilitated not to leave the trial completely, even though they no longer receive the trial treatment. If, however, the participant exercises the view that they no longer wish to be followed up either, this view must be respected, and the participant withdrawn entirely from the trial. The reason for withdrawal will be documented in the trial database.

A study withdrawal form will be completed detailing how the participant / responsible clinicians communicated their wishes to withdraw, type of withdrawal, date, reasons (if obtained), any discussion regarding withdrawal and onward referral, if clinically necessary by the MHSW. All necessary records and databases will be updated to reflect the withdrawal status of the participant.

Data already collected will be kept and included in analyses according to the intention to treat principle for all participants who stop follow up early and this will be made clear within the information sheet and if/when participants discontinue treatment / withdraw.

Participants who discontinue treatment / are withdrawn or choose to stop trial follow-up early will not be replaced.

The trial management group, DMEC and TSC will be made aware of withdrawals and any reasons obtained. These should be considered as part of the meeting agenda and any themes identified and acted upon.

Attempts will be made to contact the young person if they do not attend the intervention sessions. If no response is received from the young person the parents/guardian of the young person will be contacted to try to ascertain why the young person has not attended. If the young person no longer wishes to have any contact, they will be recorded as loss to follow up.

After the final assessments, their GP will be notified that their involvement in the study has ended.

An end of study form will be completed for all participants who complete the last follow up assessment. The date of their last assessment will be the date they completed the study. The person completing this form will be required to confirm that the referring service (or their GP, if self-referred) has been advised that they have finished in the study.

End of Trial

The end of trial will be when all participants have completed all scheduled assessments and all questionnaires/data items have been completed and interviews taken place. This is scheduled to be 26 weeks after the baseline measures were completed.

A declaration of end of study form will be completed and sent to the REC within 90 days of the end of the study.

Sample size justification

Sample size

Eighty-one eligible young people at three sites (27/site) with mild to moderate depression based on 2016/2017 data from Hertfordshire & Norfolk CAMHS, and from primary care practices. This sample size was selected to enable more than 20 patients per arm and allow for each of the three interventions to be completed at each of the three study sites, giving nine groups in total. Each group needs to be at least nine patients to provide the best chance that at any given session at least six patients are present (allowing for 1/3rd no show).

As this is a feasibility study it is not powered to detect a difference in clinical outcome between the two interventions. Therefore, no power calculation has been performed. We have estimated that a total sample size of 81 patients will be sufficient to estimate the recruitment rates and completion rates.

Feasibility

Feasibility Data

A traffic-light system, relating to recruitment, retention, adherence and completion will inform whether we "stop", "proceed" or "proceed but with protocol changes" [74]. A final report for the feasibility study will be provided to the NETSCC, and commencement to the next phase undertaken once the report has been agreed In the feasibility phase the following criteria will be used to monitor and assess suitability of participants, acceptability and completeness of trial measures using the methods of collecting this information described elsewhere.

Referrals & Recruitment:

- Three sites providing mental health services to young people, recruited to the study
- Identification of 30 to 50 patients per month from record screening at CAMHS and GP Practices at each site
- Referring 16 to 20 patients per month at each site for screening for eligibility to join the study
- More than 10% of eligible young people identified from record screen recruited
- Identify referral patterns at each site
- Identify and engage with an additional five sites willing to participate in the main trial (based on referral data)
- Exploration of barriers to recruitment based on demographic patterns (e.g. religion, gender, ethnicity, Socio-Economic status) and how these will be addressed

Acceptability:

- Acceptability of interventions to young people
- Young people's attendance at sessions to be more than 66%
- REPs and MHSWs willingness to deliver sessions and encourage engagement of young people in the groups
- Acceptability of training to REPs and MHSW's

Completion of trial measures-

- More than 80% of main outcome measures completed at 14 weeks
- Successful completion of resource use data for 80% of patients at baseline and 26 weeks
- Average and peak heart rate during the sessions (weeks 4 & 8, ±1 week), and accelerometer data (weekly light, moderate and vigorous physical activity, and sitting) can be collected at 14 and 26 weeks.

The findings will be used to refine the intervention and study delivery for the full-scale trial.

Process Evaluation

A parallel process evaluation will be conducted using mixed methods including observations of intervention sessions, semi-structured interviews, review of intervention log sheets and case report forms and focus groups. The emphasis will be on examining intervention delivery and contamination between arms, barriers and facilitators to engagement of young people and to evaluate recruitment methods. The findings will be used to refine the intervention and study delivery for the main trial.

Approximately 30 potential participants across the three study sites will be invited to take part in an interview to discuss their experience of the recruitment process. These activities will be undertaken to: (i) identify barriers to recruitment; (ii) offer an additional qualitative data set to supplement the findings of the process evaluation; and (iii) inform the development of a communication skills training package for the main trial.Independent observations will be undertaken of approximately 5-10% of the intervention sessions. Observers will use an observation checklist to ascertain fidelity to the training. We will also observe the training sessions. REPs and MHSWs will be asked to complete an intervention log together after each intervention session, including numbers of young people attending, activities undertaken and duration of each activity. Log sheets will be rated by members of the study team to identify implementation, and any potential contamination between arms.

One focus group per site will be carried out with 8-12 young people after they have completed their intervention sessions. Purposive sampling will be used to invite a diverse mix of young people to the focus groups. A semi-structured schedule will be produced to guide discussion, and this will explore acceptability of the intervention and study methods, and barriers and facilitators to participation. Focus groups will be audio-recorded and transcribed verbatim.

One focus group per site will be undertaken with professionals delivering the intervention and all REPs and the MHSWs involved in intervention delivery will be invited. A semi-structured schedule will be produced to guide discussion, and this will explore experiences of intervention training and delivery. Focus groups will be audio-recorded and transcribed verbatim.

Case report forms will record young people's reasons for declining to participate in order to inform recruitment strategies in the main trial. Non-identifiable demographic information such as ethnicity and

gender will also be recorded. Description of particular strategies within localities developed by Activity Partnerships to support recruitment of hard to reach patient groups will be evaluated.

Data Collection, Management and Analysis

Data Collection

Data collection will be by direct online entry of data onto the central database, stored on servers based at NCTU by members of the READY trial team working within each research site. If a young person is unable or unwilling to complete study outcome measures themselves, this can be done with the support of the MHSW or the REP (e.g., by having the questions read to them). Data may be entered onto paper Case Record Forms (CRFs) prior to entry onto the database. Staff will receive training on data collection and use of the online system.

Data collection, data entry and queries raised by a member of the READY trial team will be conducted in line with the NCTU and trial specific Data Management processes.

Identification logs, screening logs and enrolment logs will be kept at the trial site in a locked cabinet within a secured room or electronically on a secure server.

Clinical trial team members will receive trial protocol training. All data will be handled in accordance with the Data Protection Act 2018.

Data Management

Participants will be automatically assigned a unique study Participant IDentifier (PID). Data will be entered under this identification number onto the central database stored on servers based at NCTU. Randomisation of participants will also be implemented within this database.

The database will be username and password protected and only accessible to members of the READY study team, and external regulators if requested. This access to the study database is controlled and administered by NCTU Data Management. The servers are protected by UEA firewalls and anti-virus products and are patched and maintained (including back-ups) according to best practice. The physical location of the servers is environmentally controlled and protected by CCTV and security door access.

The database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data.

After completion of the study, the database will be retained on the servers of NCTU for on-going analysis of secondary outcomes.

After completion of the study, the study database and associated design documentation will be routinely archived for a period of 10 years unless otherwise advised by the TMG.

Data Analysis

Data analysis for the feasibility study will be largely descriptive. The referral, recruitment and retention will be evaluated using standard reporting following the CONSORT (Consolidated Standards of Reporting Trials) criteria, reporting the proportions (and confidence intervals) of young people reaching each stage of the study, by referral source and study arm. Reach and representativeness will be described in relation to the proportions of patients who are screened for participation and are randomised, and in comparison, to the characteristics of local populations. Adherence will be assessed through the

proportions of sessions attended, the average heart rate (weeks 4 & 8 ± 1 week) achieved compared to the target for the intervention, and maintenance of exercise the extent to which young people increased exercise beyond the interventions sessions (accelerometer data at 14 and 26 weeks). Accelerometer data will be reported as time spent in sedentary, light, moderate, and vigorous activity. Feasibility of collecting outcome and resource use data will be evaluated by estimating the proportions of missing data in each of the outcomes assessed. To monitor safety, the number of adverse events will be reported by study arm.

The number of adverse events will be tabulated by group and, if appropriate, compared using a random effects Poisson regression.

Process Evaluation

In the feasibility study, triangulation of the analysis of the intervention logs, focus groups and case report forms will be used to describe, and examine delivery of all three arms and implementation fidelity in order to refine the intervention for the full-scale trial.

Intervention logs will be rated against the adherence checklist by members of the study team, to identify implementation fidelity, and any potential contamination between arms.

Findings from interviews with YP/parents regarding the recruitment process will be reviewed by the study team to identify barriers to recruitment. Key areas of difficulty will be identified. Throughout analysis, we will hold regular meetings between project team members to review findings, discuss emerging interpretations and develop recommendations for improving the delivery of recruitment consultations.

The focus groups will be transcribed verbatim and thematically analysed [75] using NVivo software. The findings from the focus groups with REPs and MHSWs will be synthesised with the intervention logs and intervention observations to explore implementation fidelity, and importantly to offer explanations for fidelity, or lack of fidelity, to the training. The findings from the focus groups with the young people will be considered along with the fidelity information from intervention logs and observations and quantitative adherence data (i.e. proportions of sessions attended, average heart rate and maintenance of exercise) to identify necessary modifications to the intervention for the main trial and to generate hypothetical propositions of the circumstances of successful delivery in the main trial.

We will examine reasons for declining to participate in the study and any demographic patterns amongst decliners to facilitate reach and representativeness of our recruitment strategy in the main trial. With reference to particular groups and local strategies outlined by Active Partnerships, recruitment strategies will be reviewed to aid our interpretation of recruitment figures for hard to reach patient groups, which will then inform any recommended changes to recruitment strategy in the full-scale trial to maximise reach and representativeness.

This analysis will enable us to identify contextual factors that may affect adoption, delivery, and maintenance of the intervention.

Economic evaluation

Aim: To test the methods and data collection tools proposed for the economic evaluation in the main trial.

The main trial will include an economic evaluation, conducted from the perspective of the NHS, social care, and families based on a previous trial [38, 76]. The methods proposed for the economic analysis in the full trial will be tested in the feasibility study. We will measure resources required to provide all

interventions in all three groups. Resources will include: staff time; equipment and consumables; premises hire; and staff training. In addition to these resources an effective intervention may affect the use of health and social care services, as well as costs borne by young people and families. These will be recorded by means of a modified client service receipt inventory (CSRI) by face to face or remote interview. The time frame will be the proceeding 12 to 14 weeks and will be completed at baseline, 14 and 26 weeks. The exact recall period will be adjusted in line with when these instruments will be collected in the feasibility trial. The design of this modified CSRI will be based on previous literature [76]. Part of the feasibility study will include an assessment of this instrument, including completeness and ease of use. In both the feasibility study and the main study any resources identified by the CSRI will be costed using appropriate local and national cost data.

Two economic analyses will be conducted alongside the main study. The primary economic analysis will be a cost-utility study estimating the cost per quality adjusted life year (QALY). We believe there is uncertainty over the best measure to use to estimate QALY's in this study. For this reason, we will include both the EQ-5D-5L [77] and the CHU-9D [78] in the feasibility study. Both the EQ-5D-5L and the CHU-9D [52] will be scored using appropriate published values. The analysis of the feasibility study will include a comparison of these two measures and will inform the decision as to which measure to use in the main study. These will include an assessment of how well each measure is completed, correlation between the two instruments, and correlation with the CDI-2 [44]. Both measures will be used to generate QALYs using 'area under the curve'. In the feasibility study these instruments will be collected at baseline, 14, and 26 weeks. The second economic analysis will use the study primary outcome measure of differences in CDI-2 between groups, collected at the same time points as the EQ-5D-5L. This will comprise a cost-effectiveness analysis consisting of cost per point change in CDI-2.

In this feasibility study the analysis of health economics data will be largely descriptive. We will assess the completeness of these instruments and consider appropriate modifications for the main trial where indicated.

Ethical considerations

The trial will be undertaken according to the principles of ICH Good Clinical Practice, and all relevant ethics and governance processes, including the HRA approvals. Key risks for the trial concern working with children and managing the risk of harm to study participants or others.

Before the start of the Trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial (amendments may also need to be reviewed and accepted by the NHS R&D departments before they can be implemented in practice at sites). All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

It is the Chief Investigator's responsibility to produce an annual progress report (APR) to be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

The Chief Investigator will notify the REC of the end of the trial and if the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

The process for consent is outlined in the methods above. The involvement of parents or carers will be a key focus, as for children under 16 years of age, parental/carer consent will be required. In all cases

the involvement of the parents in the study will be required, and separate consent from the parents / carers will be recorded for their involvement in the study (carer reported outcome measures). All children will provide consent to participate. In some cases the role of the parent may be taken by a legal carer (foster carer, or Social Services) and in these cases relevant consent, and engagement by carers (sometimes not the legal guardian) will be facilitated.

Risk management is a key issue for the trial and may be encountered as part of the assessments for recruitment, or as a crisis during the conduct of the study. In both cases processes will be put in place to ensure timely, and appropriate clinical support for the young people involved. Within the clinical setting the lead clinician at NSFT (Dr Wilson) will review all arrangements for the clinical management of young people in the study. PIs at each study site will be responsible for developing a local treatment protocol to manage clinical risk. As part of the recruitment process, if significant risk of harm to the young person or others is identified, the young person will be urgently referred to normal assessment / service crisis support pathways involving any current care teams / GPs. For young people who present with a significant crisis during the study the young person will be provided with information relating to out of hours crisis provision. The event will be reported to the sponsor, Trial Manager, CI and Dr Wilson, and the study team will ensure that appropriate local review and support has been provided for the young person.

Young people who present significant risk of harm to themselves or others (as assessed by the CDI 2>36 [79], DAWBA [45]) will be referred back to the service that referred them (or to their GP if they self-referred) and will not be able to join the study. Assessments using the DAWBA will in particular identify specific risk factors (psychosis, substance abuse, suicidal ideation) that might exclude the young person from the study. The PI in the NHS service at each site will oversee this process to ensure that the young person is referred back to the clinical practice that referred them for further assessment and treatment, according to local site protocol. If the young person self-referred, then they will be referred to their GP.

The REPs and the MHSWs are the point of contact for the young people in the study. Following the relevant study and mental health training, these staff will be provided with monthly supervision by the local PI or local delegate. The DMEC and TSC will monitor and review adverse events every four months, and the TMG will do so monthly.

Crisis information will be available for young people, facilitators of the intervention and parent or carers. The local PI is responsible for identifying the correct clinical local routes for next steps.

Parent and carer involvement will be encouraged through engagement in the study assessments, and by providing an information pack about the intervention and the study. The content of the pack will also provide standard information about depression in young people, crisis cards and the potential value of exercise in reducing depression. The pack will help the parents to support the young person during and after the intervention.

Quality Assurance and Control

Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the READY trial are based on the formal Risk Assessment performed, that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

Central Monitoring

NCTU staff will review Case Report Form (CRF) data for errors and missing key data points. The trial database will also be programmed to generate reports on errors and error rates. Essential trial issues, events and outputs, including defined key data points, will be detailed in the READY trial Data Management Plan.

On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the READY Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports.

Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits and REC review, by providing access to source data and other trial related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the READY Quality Management and Monitoring Plan.

Public and Patient Involvement

Young people and members of a PIRg have been actively involved in the development of this study. At Stage 1 we consulted with young people with depression from a local Youth Council, aged 14-15 years, who have experience of receiving care from a local CAMHS. In addition, a PIRg at the University of Hertfordshire reviewed the application and made helpful suggestions. The combined comments and advice shaped key aspects of the proposal. For Stage 2 we returned to the local Youth Council with more focused questions addressing the key areas highlighted by the HTA panel. We also consulted with a LGBTQ (Lesbian, Gay, Bisexual, Transgender, Queer) group of young people (16-19 yrs) and an ethnically mixed group of young women from Luton aged 15-17 yrs, to help us consider the complexity of gender in relation to exercise and depression and to enhance inclusion and diversity in our PPI.

We have a strong PPI strategy in place to involve young people, parents and carers, and members of the public in key discussions and decisions throughout the study. We will do this through the establishment of a YPAG, consisting of 18 young people with depression, who will meet three times a year, shortly

before the Steering Committee, so that the views of the young people are incorporated into the key decisions. The YPAG will be run in consultation with the young people themselves and aligned with examples of good practice of involving young people in research from INVOLVE. We will also recruit three parents or carers of young people with depression to the Steering Committee from local parent/carer groups. PIRg members will also sit on the Steering Committee and support the induction and training of parents and carers and the YPAG and to be PPI 'mentors'. At different stages of the research we will involve our PPI contributors in workshops for data analysis and interpretation, writing and dissemination activities. We will record all PPI activity, meetings and workshops so that we can report on the impact of the PPI in future reports and publications.

Protocol compliance

Although steps will be taken to avoid it, accidental protocol deviations may happen at any time. They will be adequately documented on the Protocol Deviation forms (see appendix 2) and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

Data Protection and patient confidentiality

All investigators and trial site staff will comply with the requirements of the General Data Protection Regulation (GDPR) and the UK Data Protection Act 2018 as well as the University of Hertfordshire University Policies and Regulation document "Data Management Policy" and the Norfolk and Norwich University Hospital NHS Trust/University of East Anglia Joint Research Office SOPs.

An electronic case report form will be produced. Each participant will have a corresponding Case report files (CRF) unique to them. CRFs will not bear the participant's name. The participant's initials, date of birth and study PID will be used for identification on the database. Access to the database will be managed by NCTU and will be restricted and controlled to authorised personnel and will be password protected. The audit trail will be monitored regularly for any unauthorised access. It is the responsibility of the CI/PI to ensure that relevant personnel are delegated to carry out data collection and data entry. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

Dissemination Policy

The TSC have responsibility for ensuring effective dissemination of the study results. The guidance below will be followed when preparing material for dissemination:

The role of the NIHR

DHSC and NIHR require that NIHR-funded researchers publish their main study findings in a peer-reviewed, open access journal.

- When submitting an article for publication, the NIHR's contribution must be acknowledged in full.
- Research articles, papers and reports should not use the NIHR logotype, but must use a statement acknowledging funding/support together with the NIHR disclaimer.
- Therefore, the following text should be included in articles and reports:
  This study/project is funded by the NIHR under its Health Technology Assessment programme (project reference 17/7810). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.
- The NIHR programme manager should be informed of all accepted journal articles resulting from the study.
- A copy of the final manuscript of any research papers supported in whole or in part by the NIHR should be deposited with Europe PMC upon acceptance for publication, to be made freely available as soon as possible and in any event within six months of the journal publisher's official date of final publication to meet the NIHR open access commitment.
- The NIHR and the Department of Health reserve the right to use data or other material from projects that it funds for policy development and publicity activities. The NIHR and the Department of Health may publicise the outcome of NIHR-funded research studies through its website, in publications and in press releases where appropriate.

Expected output and impact

A publication policy will be written and submitted for approval to the TSC.

The immediate output will be that the results of this feasibility study will be used to inform the progression to a full study. The TSC will make a recommendation about the feasibility of a full-scale study depending on whether the feasibility progression criteria have been met, and/or whether there is evidence to suggest that the design of the study could be improved.

Our research will provide essential evidence to determine whether exercise of a high and, or low intensity is a clinical and cost-effective intervention for help-seeking adolescents with depression, providing valuable information for the NHS, policy makers and commissioners. The trial methodology and findings will be disseminated widely through high impact international peer-reviewed journals, the HTA/NIHR, and at conferences for clinicians, commissioners and researchers working in CAMHS, primary care, public health, Local Authorities, CSPs and voluntary organisations.

The study team will engage with a wide range of stakeholders. PPI will be embedded in the study, and with input we will develop a project website and social media presence to inform and engage young people and their families, clinicians, NHS providers and commissioners, and the wider population about the progress, findings and impact of our research. Our YPAG will help develop meaningful and appropriate ways of telling young people about our research, based on previous research conducted with young people with depression by colleagues [80]. We will present our findings to referring clinical teams, GP practices, NHS providers and commissioners, CSPs, schools, youth groups, voluntary organisations and other partnership groups in the research localities.

Engagement with society, health and public health to ensure utilisation of the trial outcomes is key. If exercise is found to be a clinical and cost-effective intervention for adolescents with depression, an exercise intervention could be considered for inclusion in routine clinical care, such as 'exercise on prescription' schemes currently prescribed by GPs. To facilitate this, we would work closely with the NHS England's Children and Young People's Mental Health Improvement teams to ensure that the

research findings are disseminated through clinical networks to Local Transformation Plan (LTP) leads, commissioners and providers. Through these networks the research will shape a wide range of community-based public health and wellbeing programmes for this age group (13-17 years) with and without depression, including school-based physical activity programmes, Active Partnerships, Sport England funded Satellite Clubs and other youth organisations.

It is anticipated that a positive outcome will be incorporated in relevant NHS clinical guidelines (e.g. NICE CG28), and wider NHS and public health policy around the health and wellbeing of young people. A negative outcome for the trial would also be an important output and will refocus current practice and future research, depending on the nature of our findings.

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