StratCare-2

StratCare Trial 2: Evaluating the clinical and cost-effectiveness of AI-driven stratified care for depression

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StratCare Trial 2: Evaluating the clinical and cost-effectiveness of AI-driven stratified care for depression.

This document describes a clinical trial and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to sites participating in the trial.

Authorisation Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the ICH GCP guidelines, CTRU (and/or any other relevant) SOPs, and other regulatory requirements as amended.

I 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.

I also confirm that I 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.

Protocol authorised by:

Name, Role and Organisation	**Signature**	**Date**
Chief Investigator		
Sponsor		
Statistician		
Study Manager		

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Abbreviations

Definition of terms

AD-SUS	Adult Service Use Schedule
ADE	Adverse Device Effect
AE	Adverse Event
AESI	Adverse Event of Special Interest
AI	Artificial Intelligence
CCC	Confirmation of Capacity and Capability
CI	Chief Investigator
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
CTRU	Clinical Trials Research Unit
DD	Device Deficiency
DMEC	Data Monitoring and Ethics Committee
EQ-5D-5L	EuroQol Five Dimension Assessment
GAD-7	Generalised Anxiety Disorder Assessment
GCP	Good Clinical Practice
IAPT	Improving Access to Psychological Therapies
ICH	International Conference on Harmonisation
ISF	Investigator Site File (This forms part of the Trial Master File)
NHS	National Health Service
NHSFT	NHS Foundation Trust
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
PIS	Participant Information Sheet
PPIE	Patient and Public Involvement and Engagement
PSS	Personal and Social Services
PSSRU	Personal and Social Services Resource Use Database
QALY	Quality-Adjusted Life Year
RCSI	Reliable and Clinically Significant Improvement
RCT	Randomised Control Trial
REC	Research Ethics Committee
ReQoL-10	Recovering Quality of Life Questionnaire
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAPAS	Structured Assessment of Personality Abbreviated Scale
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TWIC	Trial Within a Cohort
USC	Usual Stepped Care
WSAS	Work and Social Adjustment Scale

1. General information

1.1 Investigator details

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1.4 Role of the Funder

The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication. The funder has approved the selection of members for oversight committees.

1.5 Protocol amendments

Date	Reference	Protocol Version	Details

Trial Summary

Study title	StratCare Trial 2: Evaluating the clinical and cost-effectiveness of AI-driven stratified care for depression
Short title	StratCare-2
Sponsor	Rotherham Doncaster and South Humber NHSFT (RDaSH)
Funder	NIHR Health Technology Assessment (HTA) Programme
clinicaltrails.gov	**NCT06567340**
Project start date	October 2023
Project end date	May 2027
Hypothesis, aims, and objectives	**Hypotheses:** - Stratified care will result in lower mean depression scores compared to usual stepped care (USC). - Stratified care will result in a statistically significant higher proportion of cases with reliable and clinically significant improvement in depression symptoms, compared to USC. **Aims**: - To evaluate the clinical and cost-effectiveness of AI-driven stratified care for depression symptoms in adults by comparison to stepped care. **Objectives:** a) To evaluate the clinical effectiveness of a stratified care pathway for patients with depressive symptoms, where psychological treatments are selected using an AI-driven algorithm, by comparison to USC. b) To evaluate the cost-effectiveness of AI-driven stratified care. c) To evaluate the longer-term outcomes measured at 18-months post-enrolment. d) To systematically identify barriers and facilitators of implementation and adherence to AI-driven stratified care.
Trial design	A pragmatic, single-blind, multi-site, parallel group cluster RCT, with an internal pilot and qualitative, health economic and process evaluation sub-studies.

Internal pilot/feasibility criteria	Green = 100% (n=493 overall; n=31/team) participants by month 15 = continue to main trial. Amber = 50%-99% (n=246-492; n=15-30/team) participants by month 15 = review study for continuation. Red = Less than 50% (n≤245; n≤14/team) participants by month 15 = triggers a discussion about continuation with the DMEC.
Setting	NHS Talking Therapies Services, England
Participants	Participants are adult patients with case level depression symptoms seeking and eligible for treatment for common mental health problems in Talking Therapies services. **Inclusion criteria:** ▪ 18 years of age or older. ▪ Patients who consent to share their de-identified clinical records for research purposes. ▪ Patients assessed as eligible for psychological care in Talking Therapies based on clinical guidelines. ▪ Patients with case-level depression symptoms (PHQ-9 ≥ 10). **Exclusion Criteria:** ▪ Those who are ineligible for treatment in Talking Therapies services according to standard treatment guidelines.
Intervention & control groups	Intervention – Treatment recommendation made by the StratCare-2 App using stratified care principles. Control – Treatment recommendation made using usual stepped care principles.
Primary outcome(s)	Depressive symptoms, as measured by PHQ-9, at 12 months post baseline.
Secondary outcome(s)	Anxiety symptoms, quality of life / quality-adjusted-life-years at six, 12 and 18 months, depressive symptoms at six and 18 months
Duration of recruitment period and first enrolment date	Nine months, Planned September 2024
Duration of follow-up	18 months post-enrolment

Target sample size	1252
Definition of end of trial	Last participant last visit

The study will be conducted in accordance with the protocol and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

2. Introduction

2.1 Background

Over a million NHS patients access psychological treatments in primary care each year, which are currently delivered in a stepped care model [1]. In stepped care (from now on referred to as Usual Stepped Care, USC), patients initially access low-intensity interventions that last up to eight sessions, and later can access more intensive, costly and lengthy psychological therapies (up to 20 sessions) if needed. In theory, USC is a "self-correcting" model, which allows patients to access the treatment that meets their needs [2]. However, in practice, patients with more complex problems can wait several months (or more) to access the appropriate treatment. Because of the requirement to start with a low-intensity intervention, their symptoms can get worse during this time, and they end up having a more protracted treatment pathway. Some of these patients drop out of treatment early, without the opportunity to access appropriately intensive treatments [3]. Patients with complex needs (i.e., multiple long-term conditions, poor functioning, chronic interpersonal problems) often experience socioeconomic adversity (e.g., joblessness, discrimination) and poor access to care. An alternative way to organise psychological treatments is using a stratified care model, where patients are matched to the most appropriate treatment for their needs. Stratified care is based on principles of precision medicine [4], and seeks to offer "the right treatment, to the right patient, at the right time". This study aims to evaluate the impact of stratified care in NHS Talking Therapies services, where available treatments are selected and recommended in a personalised way, using an artificial intelligence (AI) technology called "StratCare". The clinical- and cost-effectiveness of this AI-driven stratified care model will be compared with USC using a pragmatic, single-blind, multi-site, cluster randomised controlled trial design.

2.2 Rationale

Mental health problems impose an enormous burden on individuals and healthcare systems. Depression is currently the first cause of disability, with >300 million individuals affected around the world [5], and it often co-exists with anxiety problems. Without treatment, depression and anxiety symptoms can become chronic for one in two people and can accelerate the chances of death from many causes including physical illnesses and suicide [6]. In the UK, around one in six adults have common mental health problems, with an estimated cost of £1.7 billion/year in healthcare, benefits and lost productivity; and this is projected to reach £3 billion/year by 2026 [7]. Of all people on incapacity benefits in the UK, 38% are directly related to mental health problems. If patients on benefits were to access effective mental health care, the cost of their treatment would be recovered after one month of them being employed [8]. There is a strong case for investment in innovations that could enhance psychological care for these high-prevalence and high-impact conditions, since even a marginal improvement in the effectiveness of care could help to reduce health-related inequalities and disability for some of the most disadvantaged people. Furthermore, technologies that help to make rapid and evidence-based decisions could help to make

psychological treatment pathways more efficient, potentially reducing waiting times and provide cost-savings.

A recent review concluded that depression treatment outcomes could be improved using personalised treatment selection, where patients are optimally matched to available treatments [9]. However, this evidence comes from retrospective analyses of clinical trials, and prospective demonstrations are still lacking. Informed by this literature, studies from our group [3,10] and from other groups [11,12] have replicated the finding that some patients with specific features are more likely to recover from depression if they access high-intensity psychological therapies, while other patients can recover after low-intensity interventions. The features that help to differentiate these distinctive subgroups of patients include clinical (e.g., symptoms, personality traits) and sociodemographic features (e.g., employment status) that can be collected in a quick, standardised, and inexpensive way during routine clinical assessments.

Our research team developed an advanced machine learning algorithm that combines these features to classify patients into distinctive subgroups (phenotypes) of cases that respond differentially to low- versus high-intensity treatments. Using observational data from 1,512 patients who accessed USC treatments in the NHS, we developed a clinical prediction model in a training dataset and validated its predictive accuracy in a statistically independent test dataset [10]. This proof-of concept study indicated that applying stratified care in routine practice improved treatment outcomes, simply by assigning patients to available interventions in a personalised way, based on information that is readily available at the time of initial assessments, using a validated clinical prediction model. We then used a comprehensive co-production process involving NHS patients and therapists to co-design an AI technology (StratCare) which easily enables clinicians (a) to collect standardised assessment data, (b) to input assessment data into an online survey form, (c) to combine this information using a machine learning algorithm and (d) to output a treatment recommendation, which can be accepted or rejected by the patient.

This extensive Patient and Public Involvement & Engagement (PPIE), consultation and technology development work paved the way for an experimental test of the StratCare concept. Our research team conducted the first prospective, large-scale, multi-site randomised controlled trial of an AI-driven stratified care model for depression and anxiety [13]. This trial included 951 adult participants who were either assigned to treatment using a stratified care model or a USC model at the time of their initial assessment upon entry into the participating services. As part of routine care, their depression and anxiety symptoms were measured at every treatment session using the PHQ-9 depression questionnaire, from baseline assessments until the end of their treatment pathway (last recorded treatment contact).

After comparing these routine outcome assessments between treatment groups in the trial, the results indicated that AI-driven stratified care significantly improved depression recovery rates (52.4% vs. 45.1%; Odds Ratio = 1.45 [1.08, 1.94] p = .01). Secondary analyses indicated that this effect was especially pronounced for patients who accessed low-intensity treatments (around 16% difference in recovery). The large sample and rigorous experimental design applied in routine care services offer strong evidence of efficacy. Nevertheless, this trial was limited by a lack of longer-term follow-up and relevant health economic measures, such as quality of life and service utilisation data. We do not know if such treatment gains may be stable after the end of treatment, which in many cases only lasts a few sessions. Furthermore, the study included only four psychological therapy teams

in the north of England, and participating therapists were highly motivated to take part in the trial, which may be atypical of wider psychological services around the country. Therefore, a multi-site trial across all regions of England, with longer-term follow-up and cost-effectiveness data would provide definitive evidence to inform clinical guidelines and NHS service policy. The primary focus of this trial is the *treatment selection process* (e.g., stratified vs. USC), which will be recorded and monitored for adherence. Stratified care is a pathway-level intervention, that if implemented would guide treatment decisions for all patients with depressive symptoms, regardless of their primary diagnosis.

2.3 Setting

Talking Therapies is a government-funded national programme of psychological services implemented in England since 2008 [14]. According to the latest annual report, this programme currently receives 1.8 million referrals per year across 158 treatment providers (organisations) [1]. Talking Therapies services are characterised by three key features [15]. First, these services offer access to evidence-based psychological interventions that are supported by clinical guidelines for the treatment of common mental health problems including depression, post-traumatic stress disorder, obsessive-compulsive disorder, phobias, and other anxiety-related disorders. Second, these interventions are organised in a USC model where most patients initially access low-intensity (brief) self-help-oriented interventions. Some patients go on to access high-intensity (lengthier) interventions if they remain symptomatic after the initial step, or if they present with more severe conditions. Third, Talking Therapies services collect clinical and demographic information including patient-reported outcome measures completed on a session-by-session basis, enabling the monitoring and evaluation of clinical outcomes. Low-intensity interventions are based on principles of cognitive behavioural therapy (CBT) and involve learning coping skills with the support of a qualified psychological wellbeing practitioner for up to eight (half-an-hour) sessions. These interventions can be delivered as individual guided self-help, in group settings, or as telephone-guided computerized CBT. High-intensity interventions are lengthier (up to 20 one-hour sessions) interventions including CBT, person-centred experiential therapy, interpersonal psychotherapy and other evidence-based psychological therapies. These interventions are delivered by clinicians qualified to a postgraduate level, following structured treatment protocols endorsed by national guidelines and under regular supervision (equivalent of one hour per week). Consistent with the pragmatic trial design, we will not record, monitor or modify these interventions in any way, so as to preserve the integrity of routinely delivered psychological care.

2.4 The technology

The StratCare app is a technology that collects data, processes inputs using a machine learning algorithm, and outputs a personalised treatment recommendation using automated decision rules. The inputs for the algorithm include patient-reported measures of depression [16], anxiety [17], functional impairment [18], personality traits [19], employment status and ethnic background. The algorithm calculates an expected prognosis (i.e., a probability of full remission of depression and anxiety symptoms after treatment), based on which patients are classified as standard (better expected prognosis) or complex cases (poorer expected prognosis). Standard cases are matched to low-intensity treatments and later have the option to move to high-intensity, if necessary, whereas complex cases are matched directly to high-intensity treatments. The rationale is to offer more intensive treatments to patients with higher risk of poor treatment outcomes, consistent with principles of stratified medicine [20].

The machine learning algorithm that is central to the StratCare app was developed using data from 1,512 patients treated in Talking Therapies psychological services. Using a split-

half cross-validation method, the model was developed in a training sample (N=755) and its generalisability was verified in a statistically independent validation sample (N=757). The training sample was analysed using a supervised machine learning method called LASSO regularization (*Least Absolute Shrinkage and Selection Operator*) [21], with bootstrap resampling to perform variable selection and weighting [22]. Predictors entered into the analysis included patients' demographic, personality and clinical features. The outcome of interest was full remission of depression [16] and anxiety [17] following treatment. Further details about the data-sources, model development and external cross-validation are available elsewhere [10]. In addition, the StratCare app was programmed to implement decision rules that would ensure compliance with national clinical guidelines [15] for the treatment allocation of patients with specific disorders (e.g., post-traumatic stress disorder, social anxiety disorder) that are only treated with high-intensity psychotherapies in the Talking Therapies system. After automating the algorithm and decision-rules in the StratCare app, we evaluated the clinical effectiveness of this method of treatment selection in a randomised controlled trial including N=951 patients [13]. As described above, the results indicated that AI-driven stratified care significantly improved depression recovery rates by comparison to usual care in Talking Therapies services. To date, this is one of the first research programmes that fully traversed the full development pathway for AI technologies (see Figure 1 below), with underpinning evidence *type i* (e.g., evidence of good fit to a training sample) through *type iv* (e.g., evidence of effectiveness in a clinical population).

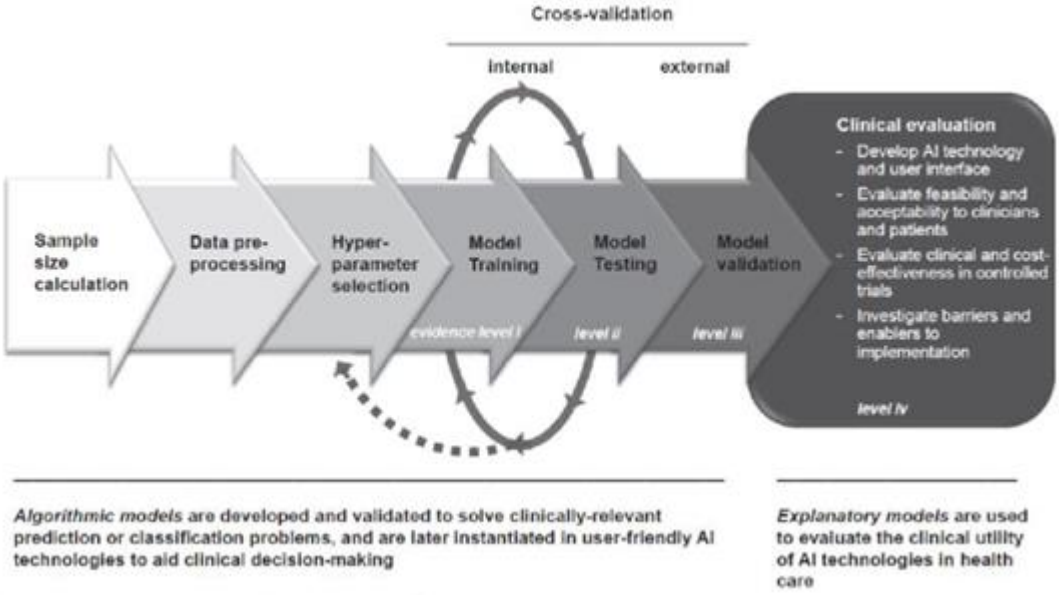


Figure 1: Steps of a development pipeline for the clinical implementation of AI
Source: Delgadillo & Atzil-Slonim 2022, Encyclopaedia of Mental Health, 3rd Ed. [24]

3. Aims and objectives

3.1 Hypothesis

- Stratified care will result in lower mean depression severity compared to USC.
- Stratified care will result in a higher proportion of cases with reliable and clinically significant improvement in depression symptoms, compared to USC.

Based on our previous proof-of-concept trial, we expect that between-group differences in depression scores will be statistically significant at follow-up (2-points difference in the full sample), resulting in a 7% higher recovery rate in the stratified care group for the full sample, and 16% higher in cases receiving low-intensity interventions. The hypothesised

mechanism of this effect involves the optimal distribution of highly responsive cases to low-intensity treatments and cases expected to require lengthier interventions to high-intensity treatments.

3.2 Aims

To evaluate the clinical and cost-effectiveness of AI-driven stratified care for depression symptoms in comparison to USC within NHS Talking Therapies.

3.3 Objectives

a) To evaluate the clinical effectiveness of a stratified care pathway for patients with depressive symptoms, where psychological treatments are selected using an AI-driven algorithm, by comparison to USC.
b) To evaluate the cost-effectiveness of AI-driven stratified care.
c) To evaluate the longer-term outcomes measured at six, 12 and 18-months post-enrolment.
d) To systematically identify barriers and facilitators of implementation and adherence to AI-driven stratified care.

4. Trial Design

A pragmatic, single-blind, multi-site, parallel group cluster RCT, with an internal pilot and stop/go criteria for progression to the full RCT. We will recruit 1252 adult patients seeking treatment for common mental health problems who present with case-level depression symptoms on the PHQ-9 measure. They will be recruited from 16 services in the NHS Talking Therapies programme across England.

Cluster randomisation will be used to allocate Talking Therapies Teams and their patients to either StratCare or USC arms. Sites may have one or more Talking Therapies Teams participating in the trial.

After GP- or self-referral for treatment, participants will undergo a standard clinical assessment by Talking Therapies clinicians, during which a treatment option will be selected. In the experimental arm, treatment selection will be guided by an AI tool (StratCare app). In the USC arm, treatment will be selected following usual clinical practice and guidelines. Participants will then follow their selected treatment option.

The total duration of the trial is expected to be 27 months, and patients will complete the trial after their 18-month post-enrolment appointment.

4.1 Blinding

Due to the design of the trial which cluster randomises at the level of Talking Therapies teams, clinicians and teams will be aware of the treatment allocation of participants for the trial. (See section 5.2 for measures to monitor for recruitment and selection bias).

Participants will be blinded to their allocation and the reason for this is explained during the consent process.

The outcome assessor will be blind to treatment allocation where possible for the duration of the trial (see section 9.2).

The trial statisticians will be blinded to allocation as per Sheffield CTRU Standard Operating Procedures (SOPs) (ST001 and ST005).

The Data Monitoring and Ethics Committee (DMEC) will have access to unblinded data at their request during the trial; this data will be prepared by the data management team in the CTRU, aided by another CTRU statistician not involved in the trial when required. The Trial Management Group (TMG) and Trial Steering Committee (TSC) data report will provide summary outcome data by Talking Therapies Team but not allocation arm, as per Sheffield CTRU SOP GOV001 and GOV002. As such, no member of the trial team other than data management will have access to outcomes in relation to the allocation arm until after database lock.

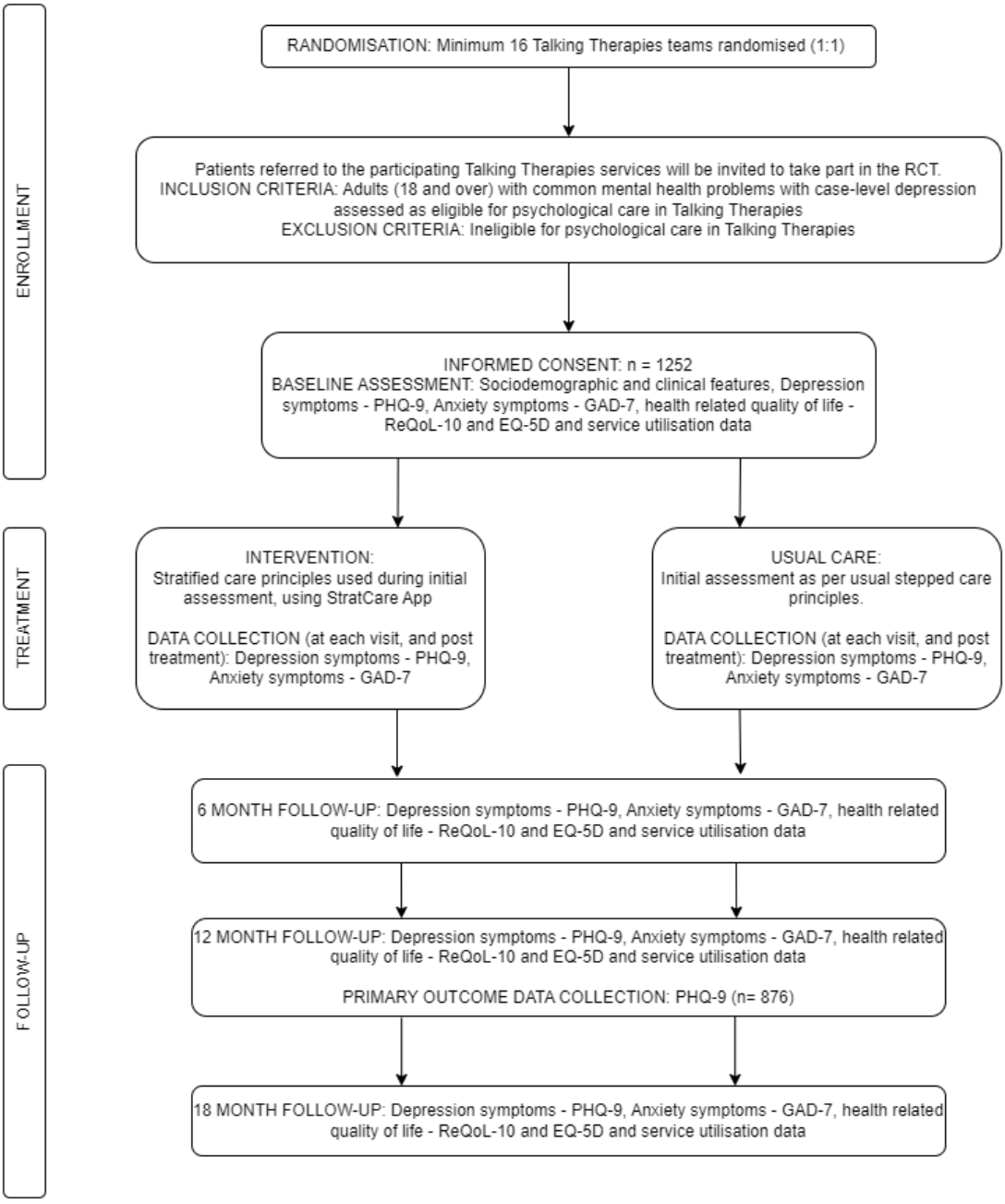


Figure 2. StratCare-2 trial Flowchart

4.2 Unblinding

It is not anticipated that an outcome assessor will need to know the treatment allocation. However, if the situation arises, site staff should discuss this with the Chief Investigator (CI) and Trial Manager. Any instances of unblinding, intentional or accidental, will be documented in full within the Case Report Form (CRF).

5. Selection of participants

5.1 Selection of teams

NHS Trusts will be recruited through a Practice Research Network, NHS data service provider (PCMIS), and other means, attending to considerations of diversity and generalisability outlined in section seven. Within trusts, individual Talking Therapies teams will be recruited to participate in the trial. Randomisation will occur at team level rather than individual level, to reduce the risk of potential contamination from clinicians becoming aware of how the StratCare app makes treatment decisions.

Individual trusts may have more than one Talking Therapies team taking part in the trial. Teams are geographically distinct with their own management structures, so it is not likely that the presence of teams allocated to both arms of the trial within a single trust represent a significant risk of contamination.

5.2 Selection of participants

Participants are adult patients seeking and eligible for treatment for common mental health problems in NHS Talking Therapies services. Patients who are eligible for treatment in the Talking Therapies service will be offered the opportunity to take part in the trial at the point of initial suitability assessment by the service, if seen by a team and clinician participating in StratCare-2.

Due to the cluster-randomised design of the trial, recruiting therapists will know the allocation of their team and so will know what treatment patients will receive prior to consent. There is the possibility of recruitment bias, and of recruiting in higher rates to one arm or the other. We will monitor approaches and recruitment to each arm, by site and therapist, in real time to observe for differences indicative of bias issues with a site or therapist. Evidence from the preceding trial suggests that there was no difference in recruitment rates between arms, and recruitment totals will be limited by recruitment targets for each team.

Neither Talking Therapies sites, clinicians nor participants will receive any financial incentive to participate.

5.3 Inclusion criteria

- 18 years of age or older.
- Patients who consent to share their de-identified clinical records for research purposes.
- Patients assessed as eligible for psychological care in Talking Therapies based on clinical guidelines [15].
- Patients with case-level depression symptoms (PHQ-9 ≥ 10).

5.4 Exclusion criteria

- Patients who are ineligible for treatment in Talking Therapies services according to standard treatment guidelines [15]. A full list of these exclusion criteria is included in Appendix 1.

5.5 Participant identification

Potential participants will be all adult patients referred into participating Talking Therapies teams at study sites. Referral processes may vary between sites, with some conducting suitability screening before the assessment appointment, and some sites screening during the appointment. Regardless of the local process, all participants referred to a participating team will be offered the opportunity to take part in the trial if they are seen by a participating clinician.

Experience from the previous trial [13] suggests that randomisation targets should be reached satisfactorily with 16 Talking Therapies Teams.

5.6 Informed consent process

The same process will be used for participants in the experimental and USC arms.

Informed consent will be received from participants during their initial assessment appointment with the treating Talking Therapies service.

At the start of the suitability assessment, participating clinicians will log in with a clinician ID and password in the StratCare App, and input the patient pseudonym (non-identifiable ID generated from the last six digits of the automatically generated ID held on the electronic patient record used in Talking Therapies sites). The StratCare App will then guide clinicians through a brief and standardised script (see Figure 3 below) to provide information and seek verbal consent from patients who they assess in routine care. We have chosen to obtain only verbal consent to minimize additional burden to make this viable within the constraints of routine care and due to the minimal risks posed by a new treatment selection method between two routinely delivered treatments.

The recruitment script will be read to all patients assessed by participating clinicians during the assessment contact. It will be made clear to patients that they will only be eligible to take part in the research if they are eligible for treatment within the Talking Therapies service. Patients will have the opportunity to ask any questions about the study and then they will be asked verbally if they provide informed consent or decline the study. Although recruiting therapists will be aware of the patient treatment allocation during the consent process, the patient will not be informed (see 4.1, 5.2).
If patients decline to take part in the research, clinicians will record the patient's ID in the 'declined' section of the StratCare App for record purposes. Patients will not be asked the reasons why they decided not to participate, to avoid any feeling of pressure or coercion.

Participants will be asked if the assessing clinician can send them further information about the study via email, text or by post, including how to opt out, how their data is used by the study, how to contact the study team with further questions and how to complain (the participant information sheet (PIS)). Participants will explicitly be advised of their right to withdraw from the study and the right to request their data to be deleted from the study dataset where possible. This link will also include information about the sub study consisting of a semi-structured interview on their views of the treatment selection process. Email will be preferable, but text or post have been included as an option for inclusion of participants

who may not communicate via email. Due to the brief verbal consent process, it is important that participants receive the PIS. If a participant declines to receive the PIS, they will be considered non-consenting and informed that they cannot participate in the trial. The StratCare App will keep a log of how many individuals are invited to participate and how many decline.

Assessing clinicians will then continue with the assessment appointment. The clinicians will record their anonymised assessment information in a secure and confidential patient record system which is used in routine care. They will record the required routinely collected screening information and the additional non-routinely collected information (see section 9) in the StratCare App.

On completion of the assessment, the assessing clinician will determine if the patient is eligible for the trial. If the patient is ineligible, the clinician will inform them that they are not eligible to take part in the research and that they will not be sent the PIS. Therapists will record in the patient notes that the patient consented but was not eligible. The appointment will then continue using normal clinical protocols.

If the participant is eligible for the trial, they will be informed of their eligibility and the therapist will confirm that they will be taking part in the research. The assessing clinician or study team will send the PIS to eligible participants only, via email or text (using a link) or post within one week of their assessment. Assessing clinicians will record informed consent and eligibility in the participant's clinical records. For consenting and eligible participants, their GP will be informed in writing of the patient's participation in the trial, as well as when they complete their involvement. Therapists will then continue to the treatment decision part of the assessment, using a scripted prompt displayed within the StratCare App. The computer program will keep a record of how many patients were eligible.

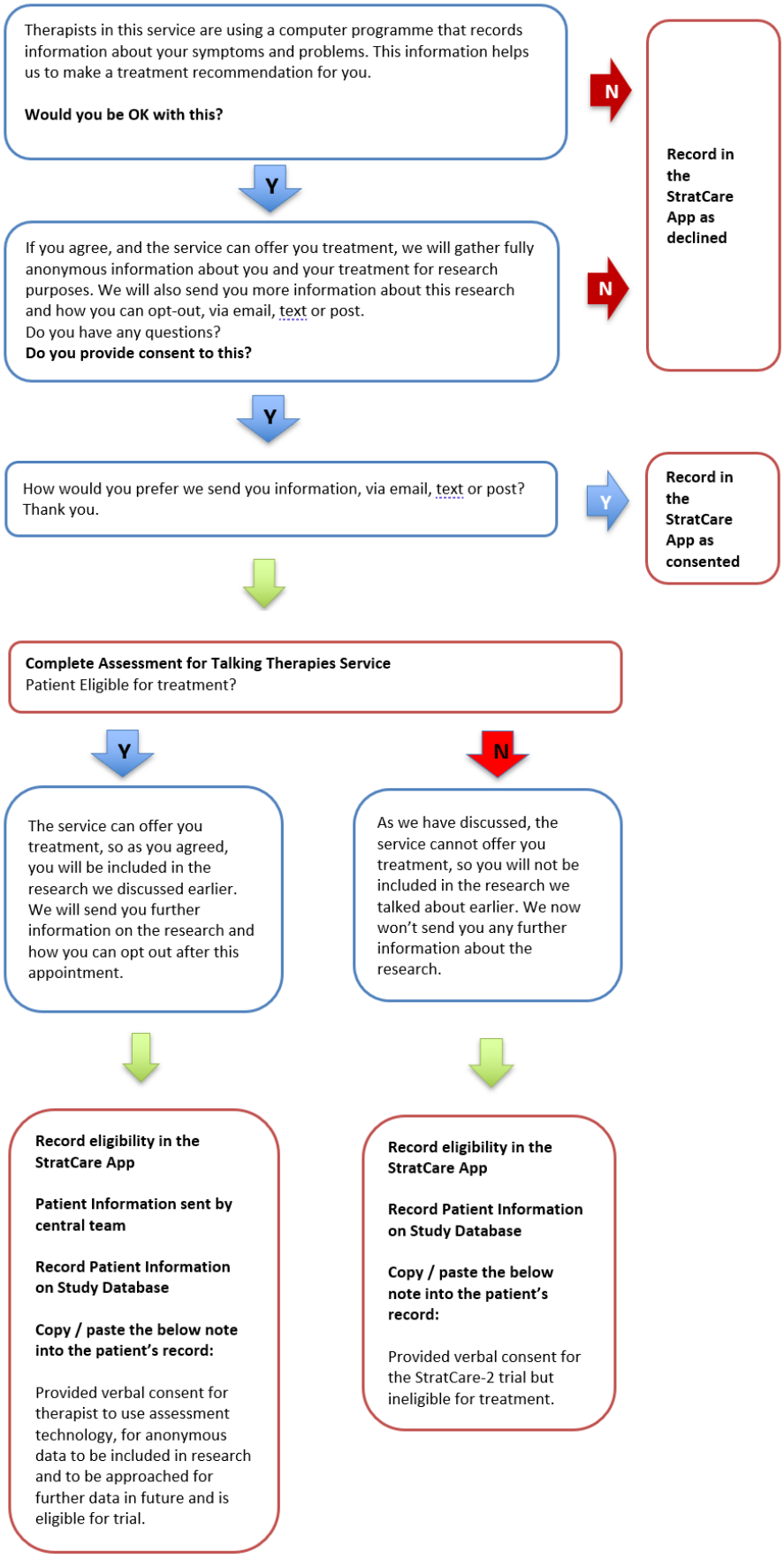


Figure 3. Consent script and process for the StratCare-2 trial

5.7 Co-enrolment guidelines

There are no restrictions on co-enrolment of patients in other interventional or pharmacological studies.

In line with clinical guidelines, participants would be expected to refrain from engaging in other psychological therapy whilst in treatment with the Talking Therapies service. Details of pharmacological or psychological interventions received by participants whilst on the trial will be recorded in the Adult Service Use Schedule (AD-SUS) measure.

5.8 Duplicate enrolment

It is unlikely that participants would be able to enrol in the trial more than once, so to minimise therapist and participant burden we will not screen for previous participation at enrolment. At the close of the trial we will cross check the personal details of participants and investigate on a case-by-case basis any suspected duplicate enrolments using clinical records. In the case of a duplicate enrolment being confirmed, we will exclude the second set of data for the participant.

5.9 Measures to retain participants and complete follow-up

Participant retention and follow-up completion will be promoted in a number of ways:

1. Participants will be provided with flexible means of returning follow-up data – by online survey, by post, by phone or video call, as per the participants' preference.
2. Evidence-based procedures for maintaining study participation and encouraging participants to complete outcome measures will be adopted; using personalised communications to contact people prior to outcome assessments, maintaining contact through study newsletters, study branding, use of up to three personalised text message or email prompts.
3. The use of short videos from the study team to engage participants and present study information.
4. Participants will be made aware in the PIS of the importance of complete datasets and the impact that missing data has on a trial [23].

5.10 Where English is not the participants' first language

The following measures are in place for where English is not the first language of participants:

1. Communication preferences will be recorded centrally for participants.
2. During the setup phase, the study team will collect information on which languages are commonly used at study.
3. Where available, translated and validated versions of measures will be collated prior to recruitment starting.
4. The PIS and other patient facing documents will be professionally translated into the required languages.
5. Where a translated PIS has not been prepared in the required language and is required by a participant, they will initially be sent an English version, and a translation will be prepared and sent to them as soon as it is available.
6. Validated, translated versions of measures and/or interpreters will be used to collect follow-up data.

6. Trial treatment

6.1 Patients randomised to experimental group

Talking Therapies teams randomised to the experimental group will implement an AI-driven stratified care treatment pathway, where patients are matched to specific treatments based on their clinical and demographic features. Patients will complete a suitability assessment with a qualified assessing clinician. They will also complete the Structured Assessment of Personality Abbreviated Scale (SAPAS [19]) measure. The assessing clinician will enter the required data from the clinical assessment, the SAPAS data, patient's previous treatment history and StratCare demographic items (see Table 2) into the StratCare app which will give a treatment recommendation of low- or high-intensity treatment. The patient and clinician discuss the assessment outcome and make a joint decision about treatment based on the StratCare App recommendation. This joint decision does **not** have to follow the recommendation of the StratCare App. The decision will be recorded in the StratCare App and clinical records, and the patient will then proceed to the waiting list for the agreed treatment. If the decision does not follow the StratCare App recommendation, the reason for this will be recorded.

6.2 Patients randomised to USC

Talking Therapies teams randomised to the USC arm will complete a standard suitability assessment for the Talking Therapies service with a qualified assessing clinician. They will also complete the SAPAS measure. The StratCare App will be used by the assessing clinician to record the necessary data from the clinical assessment, the SAPAS data, the patient's previous treatment history and StratCare demographic items but the App will **not** be used to make a treatment recommendation. Treatment recommendation decisions will be made in the usual way, following stepped care principles – where most patients initially access low-intensity treatments and can subsequently access high-intensity treatments if the first step of care is unsuccessful. The patient and clinician discuss the assessment outcome and make a joint decision about treatment based on the clinician's recommendation. The decision will be recorded in clinical records, and the patient will then proceed to the waiting list for the agreed treatment.

6.3 Psychological interventions

Whichever group the participant is randomised to, they will still access the usual evidence-based interventions available in routine Talking Therapies services. These include low-intensity guided self-help, usually lasting up to eight sessions, and high-intensity psychological therapies which can last up to 20 sessions. These interventions will not be modified in any way, to preserve the integrity of routinely delivered care.

6.4 Intervention staff

Assessing clinicians will be qualified Talking Therapies Psychological Wellbeing Practitioners (PWPs) or qualified Talking Therapies clinicians. Trainee clinicians will not participate, as their treatment decisions require validation from a qualified therapist. Talking Therapies teams will have access and training (three hours) to use the StratCare technology described above, and study processes. Assessing clinicians will also be provided with bespoke Good Clinical Practice training to cover the GCP principles required for their safe and ethical involvement in the trial, and an online portal for refresher training.

7. Randomisation and enrolment

This pragmatic cluster randomised trial will randomise Talking Therapies teams to AI-driven stratified care (experimental) or a USC (usual stepped care control) group. Randomisation at the team level is necessary to prevent contamination of the USC group through the knowledge that clinicians gain from observing which types of patients tend to be matched to low or high-intensity treatments by the StratCare model. Randomisation will be carried out by the Sheffield Clinical Trials Research Unit (CTRU), using a computerised randomisation sequence. With a limited number of 16 clusters (Talking Therapies teams) being randomised it will not be possible to stratify the randomisation by any factors.

We acknowledge that service factors such as waiting list length, the proportion of cases stepped up for high-intensity treatments, differences in socioeconomic and health indicators are known determinants of service effectiveness [13]. Data on these service factors are publicly available via NHS Digital [1] and via national statistics [24]. We will collect this information prior to the start of the trial and, where practical, purposefully recruit sites that represent a diverse cross-section of these characteristics.

As there is no patient randomisation date, the date of confirmation of eligibility is considered the baseline or anchor date for timing of the follow-up (post-baseline) assessments.

Participants are considered enrolled on the trial when both:

a) consent to participate has been received and
b) the patient has been confirmed as eligible for the study.

8. Outcomes

8.1 Internal Pilot Criteria

The following progression criteria will be applied during the first 15 months (internal pilot):
Green = 100% (n=493 overall; n=31/team) participants = continue to main trial.
Amber = 50%-99% (n=246-492; n=15-30/team) participants = review study for continuation.
Red = Less than 50% (n≤245; n≤14/team) participants = triggers a discussion about continuation with the DMEC.

We will monitor the number of participants recruited per team on a monthly basis. We expect to have all trial teams (16 minimum) recruited within the first six months of opening to recruitment. Our revised target will be to achieve 10% of recruits per team per month.

8.2 Primary outcome/endpoint

Depressive symptoms at 12 months post-enrolment, as measured by PHQ-9.

8.3 Secondary outcomes/endpoints

Anxiety symptoms (General Anxiety Disorder-7 measure - GAD-7) [17], quality of life / quality-adjusted-life-years (Recovering Quality of Life-10 - ReQoL-10 and EQ-5D) [25,26] at six, 12 and 18 months post-enrolment, depressive symptoms at six and 18 months, as measured by PHQ-9 and service utilisation data at 18 months post-eligibility.

9. Assessments and procedures

9.1 Study Assessments

9.1.1 Outcome Measures

Primary outcome: The Patient Health Questionnaire (PHQ-9) [16] at 12 months post–enrolment.

The PHQ-9 is a brief measure of depression symptoms, where each of 9 items is rated on a Likert scale from 0 to 3 representing symptom frequency in the last two weeks, yielding an overall severity score between 0 and 27 [16]. The cut-off $\geqslant$10 is recommended to screen for clinically significant depression symptoms, and a change of $\geqslant$6 points is indicative of statistically reliable change [15]. An advantage of using this measure is that all Talking Therapies patients complete it on a session-by-session basis to monitor treatment response, regardless of their primary diagnosis.

The PHQ-9 has been extensively validated in primary care populations [16], with adequate sensitivity (88%) and specificity (88%) estimates for the detection of major depressive disorder using a cut-off score ≥10.

The PHQ-9 will also be measured at six- and 18-months post-enrolment.

Secondary outcomes: Anxiety symptoms (GAD-7) [17], quality of life / quality-adjusted-life-years (ReQoL-10 and EQ-5D) [25,26] measured at six-, 12- and 18-months post-baseline, and service utilisation data.

GAD-7 is a seven-item measure of common anxiety symptoms [17]. Each item is scored on a 0–3 scale and these are summed to give an overall severity rating (range 0–21). The GAD-7 has been found to be a reliable screening tool for anxiety disorders such as generalised anxiety, social phobia, post-traumatic stress and panic disorder [17]. A cut-off score ≥8 in this measure has been shown to detect an anxiety disorder with adequate sensitivity (77%) and specificity (82%).

The EQ-5D-5L [26] measure is commonly used to derive Quality Adjusted Life Years (QALYs) in healthcare research and to ensure that cost-effectiveness analyses are comparable to other studies and health technologies. Each of the five domain items is rated on a five-point scale from ‘no problems’ to ‘extreme problems’, giving a five-digit number describing the patients’ health state. Patient responses will be converted into utility values using UK population tariff. Self-rated health is measured on a visual analogue scale from 0-100, with 100 being ‘the best health you can imagine’. As per NICE guidance, we will use the validated mapping function to derive utility values for the EQ-5D-5L questionnaire [27]. QALYs will be calculated using the trapezoidal rule for calculating the area-under-the-curve, from baseline to the 18-month follow-up.

In addition, we will also gather data on a second quality of life measure, the ReQoL-10[25], which was informed by contributions of >6,000 mental health service users. It has been developed specifically to assess quality of life in people with different mental health conditions and consists of 10 mental health questions and one physical health question. Each item is scored on a 0-4 scale and the 10 mental health scores are summed to give an overall score (range 0-40, 0 being poorest quality of life, 40 highest). A score of 24 or lower is considered as falling within the clinical range. An advantage of the ReQol-10 is that it

captures a broad range of domains including meaningful activity, belonging and relationships, control and autonomy, hope, self-perception, well-being, and physical health.

Cost-effectiveness related measures:
We will adapt the 'adult service use schedule' (AD-SUS)[28] to develop the resource use questionnaire. Resource use data will include the following: (a) primary care consultations (e.g. appointments with physician and nurse practitioners); (b) Talking Therapies resource use (i.e. number of sessions at each step along the stepped care pathway – this is routinely collected for all Talking Therapies patients); (c) use of other mental health services (e.g. consultations with psychologists, psychiatrists, community psychiatric nurse); (d) hospital visits (e.g. emergency department visits, outpatient appointments and inpatient admissions); (e) use of medications; and (f) contacts with social care (e.g. social worker, home care worker, outreach worker).

Additional data collected: In addition to the above clinical outcome measures, we will collect anonymised data for patients recruited to the trial by the participating clinicians, which is gathered in routine practice by Talking Therapies services. This data will include demographics (age, gender, ethnicity, employment status, index of multiple deprivation, self-reported disabilities) and clinical care data (diagnoses, number of therapy sessions, types of treatments offered, reason for discharge, last step accessed in stepped care system, item level data for PHQ-9, GAD-7 and Work and Social Adjustment Scale (WSAS). The rationale for this is to thoroughly describe sample characteristics and to compare the trial participants to the wider population of patients treated in the trial sites.

For therapists participating in the trial, socio-demographic data collected will include age and job role, self-identified gender, ethnicity, full postcode, current occupation, number of years since qualifying as a clinician, banding, highest level of qualification.

9.1.2 Potential risks identified during data collection

Potential risk to participants may be identified during data collection. This could be through direct interaction, or in responses to outcome measures. If a participant is still under the care of the Talking Therapies team, this risk will be communicated to the service and the risk managed by the service using standard clinical protocols. For participants who are no longer in the care of a Talking Therapies service (e.g. post-treatment), a risk management protocol will be in place to respond to risk identified by the central study team during data collection. Responses range from signposting for support, to referral to secondary mental health services (such as a Crisis Team) by a clinically qualified team member.

Item nine of the PHQ-9 asks if a patient has been bothered by 'Thoughts that you would be better off dead or of hurting yourself in some way'. If a participant responds to this with a score of 1 or greater, indicating some level of risk of self-harm or suicide, they will be prompted to complete the Columbia Suicide Severity Rating Scale (C-SSRS) Screener. Responses to this scale will be monitored. For those still in the care of their Talking Therapies team, this risk will be communicated to the service and the risk managed by the service using standard clinical protocols.
For participants who are no longer in the care of a Talking Therapies service (e.g. post-treatment), the risk management protocol will define what level of response is required based on the level of risk indicated by the C-SSRS. Responses range from signposting for support, to assessment and referral to secondary mental health services (such as a Crisis Team) by a clinically qualified team member.

9.2 Data Collection

Data will be collected in five ways, depending on the stage of the trial, the type of data being collected, whether the patient is still being treated by the Talking Therapies service, and participant preference.

a) via direct entry into the StratCare App by the assessing clinician (baseline only).
b) as part of clinical care within the Talking Therapies service, collected by Talking Therapies staff. Data collected this way will be entered into the study database by study staff, or where available using an automated download from clinical records, transferred securely using an encrypted system to the study database.
c) via an online data collection system, self-reported.
d) via paper forms, self-reported.
e) via telephone or videocall, collected by study staff.

Study staff conducting outcome assessments by method e) will be blind to allocation where possible.

Data collection windows will be +/- one month of the target date. Where more than one data point exists within the data collection window, the data closest to the target date will be used. In exceptional circumstances where data does not exist within the data collection window, data within +/- three months can be used.

Whilst participants are in treatment, there will be routine collection of the PHQ-9 and GAD-7 measures. This data will not be used for the primary or secondary analyses, unless trial-collected data is missing for those time points. In this case, the routinely collected PHQ-9 or GAD-7 scores closest to the target dates, and within the data collection window, may be used.

If participants find the data collection schedule burdensome and so wish to withdraw, they will be offered the option of providing a reduced set of measures prioritising the primary outcome, to promote data completion rates.

Beyond the AI-guided treatment suggestion made by the StratCare App in the experimental arm, patient reported outcome data will not inform the clinical care of individual trial participants.

9.3 Participant 'opt out' and participant withdrawal

Participants may wish to withdraw from receiving the trial intervention, or providing follow up data, or there may be a clinical need to withdraw the participant.

9.3.1 Opt out

Participants in Stratcare-2 provide consent through a brief verbal process. As part of this, a post consent 'opt-out' system is in place, so that once they have seen the full PIS, participants can withdraw from the trial shortly after consent and remove all their data.

After the consent and assessment appointment, participants are sent a link to the PIS, which provides further information on the study and how to opt out. If participants decide to withdraw their consent within a week of being sent the PIS (or the translated PIS if this is required), they will be classed as an opt-out, and all their information will be removed from trial records. This will be documented on a study completion/discontinuation form and the

patient notes if still in treatment, and no further data will be collected for this participant for the study. The participant's GP will be informed in writing of their withdrawal.

9.3.2 Withdrawal

Participants may withdraw their consent for the study at any time, without providing a reason for this. If this occurs after the opt-out window has closed, it will be classed as a withdrawal and documented on a study completion/ discontinuation form and the patient notes if still in treatment. Participants will be offered the option for their routinely collected clinical data to continue to be included in the trial, but to not be contacted for any further follow-up data collection. If they decline this then no further data will be collected for this participant for the study. The participant's GP will be informed in writing of their withdrawal.

The participant is not required to give a reason for withdrawal, but a reasonable effort will be made to establish this reason while fully respecting the participants' rights. Any data collected up to the point of the participant's withdrawal will otherwise be retained and used in the final analysis unless the participant requests otherwise, and this is made clear to the patient at the time of consent. If a participant requests their data to be removed, this will be facilitated where possible but it will not be possible to do so beyond the point at which data is fully anonymised.

Withdrawing participants will not be replaced.

The treatment of participants will not change if they opt-out or withdraw, they will continue with their treatment as planned.

Excessive participant withdrawal from follow-up has a negative impact on a study. Study teams will explain to participants the importance of remaining in the study for follow-up. Nevertheless, if participants do not wish to remain in the study their decision must be respected.

9.4 Study assessments schedule

	Baseline	At each therapy session	6 months	12 months	18 months
Enrolment					
Eligibility assessment	X				
Informed verbal consent	X				
Primary outcome					
PHQ-9*	X	X	X	X	X
Secondary outcomes					
GAD-7*	X	X	X	X	X
ReQoL-10	X		X	X	X
EQ-5D-5L	X		X	X	X
AD-SUS	X		X	X	X
Adverse events*		X	X	X	X

Table 1: Study assessment schedule

* - collected as part of routine care whilst participants are in the Talking Therapies service

	Baseline	6 months	12 months	18 months
Enrolment				
SAPAS	X			
WSAS*	X			
StratCare Demographic Variables* (Age, White British/Other ethnicity, Employment Status)	X			
Previous treatment received*	X			
Clinical care data*		X	X	X

Table 2: Additional data collected

* - collected as part of routine care whilst participants are in the Talking Therapies service

9.5 Loss to follow-up

Participants will be defined as lost to follow-up if they do not complete the 18-month data collection visit, despite further attempts at contact having been made. If a participant is lost to follow-up, this will be recorded in the CRF using the study completion/discontinuation form.

10. Safety Reporting

ICH-GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events in clinical studies. These procedures are described in this section.

10.1 Definitions for the StratCare-2 Trial

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a study participant. Adverse events relating to physical health will not be recorded on the StratCare-2 trial, unless they relate to physical self-harm.

Adverse Event of Special Interest (AESI)	A pre-defined adverse event that the sponsor wants to monitor carefully. In StratCare-2, the only AESI is 'Suicidal ideation **with** plans **and** imminent intent'. This should be reported as an adverse event and will be included in safety reporting alongside Serious Adverse Events.
Serious Adverse Event (SAE)	The definition of an SAE in StratCare-2 is as follows: Results in death Death by suicide Is life-threatening*, Report of physical self-harm requiring medical attention Requires admission to psychiatric hospital Results in persistent or significant disability or incapacity Referral to Crisis Care Is otherwise considered medically significant by the investigator**
Unexpected AE/SAE	An adverse event or serious adverse event which has not been pre-specified as expected.
Related AE/SAE	An AE or SAE which is related to the trial treatment.
Adverse Device Effect (ADE)	An Adverse Event (AE) related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Device Deficiency (DD)	Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling.

Table 3: Definitions for adverse events in the StratCare trial

*The term life-threatening in the definition of a serious event 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 hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.
**Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Identification of events

AEs and SAEs are defined as an event that occurs after the participant has provided informed consent for trial entry and until completion of their 18-month post-enrolment follow up.

AEs and SAEs will be identified at the six-, 12- and 18-month post-enrolment follow-ups and during routine treatment with the Talking Therapies service. However, they can be identified and reported for participants at any stage of their trial participation.

Self-report follow-up questionnaires will include questions about adverse events. Where potential SAEs are identified, site or central study team staff identifying the event will follow this up by contacting the participant or reviewing medical records. If the participant is no longer in the Talking Therapies service, central study team staff will make up to three attempts to contact the participant to ascertain further details.

10.3 Recording and reporting

When an event is identified, the process for recording and reporting outlined in Figure 4 will be followed. The local PI (or other suitably trained member of research staff who has been delegated the task) should be notified as soon as possible and will assess the event for classification as an SAE or not (see definition in Table 3).

All AEs will be recorded on the AE report form, within the participant CRF, including those that fulfil the criteria for being serious. Sites are asked to enter all available information onto the study database within one week after the site becomes aware of the event. Completed AE and SAE forms should also be filed in the Investigator Site File (ISF).

10.3.1 Serious Adverse Events

All AEs classed by the PI or delegate as serious will require more detailed information to be recorded in the participant CRF. In such cases, the event must also be reported to the Sheffield CTRU and the Sponsor within 24 hours of the site becoming aware of the event (see 10.3.5).

10.3.2 Causality of Serious Adverse Events

The StratCare-2 intervention makes a treatment suggestion between one of two routinely provided Psychological Interventions. It will not be possible to identify a causal link between the intervention and individual SAEs, so causality of individual events will not be assessed on the StratCare-2 trial. All SAEs will be considered unrelated to the intervention at initial reporting.

SAEs will be reported to the DMEC over the duration of the trial who may decide to infer causality based via the frequency of the SAE across the entire trial.

10.3.3 Expectedness of Serious Adverse Events

The PI or CI will assess if the SAE is expected or not. All of the SAEs defined in table 3 will be classified as unexpected, with the exception of the following which are classified as expected:

- Self harm
- Death by suicide
- Suicidal ideation **with** plans **and** imminent intent
- Referral to crisis care
- Admission to psychiatric hospital

10.3.4 Intensity of Serious Adverse Events

The PI or reporting person at site should assess the intensity of all SAEs. The following categories will be used to define the intensity of an SAE:

Category	**Definition**
Mild	The event does not interfere with the participant's daily routine and does not require further procedure; it causes slight discomfort.
Moderate	The event interferes with some aspects of the participant's routine, or requires further procedure, but is not damaging to health; it causes moderate discomfort.
Severe	The event results in alteration, discomfort or disability which is clearly damaging to health.

10.3.5 Recording and notification procedure for Serious Adverse Events

All SAEs should be reported to Sheffield CTRU and the Sponsor (via the emails below) immediately and within 24 hours from the point of identification. If it appears that an SAE has been reported late, this should be escalated to the PI and/or CI, recorded as a protocol non-compliance and appropriate measures put into place to monitor and review this.
The following notification procedure should be followed:

● Details will be recorded on an SAE form (filed in the Investigator site file or downloaded from the AE CRF page). It is recommended that for clarity forms are completed electronically, signatures on SAE forms can be electronic (e-signature or a typed name) or wet ink. Forms should be emailed to the following groups:

Sponsor: rdash.research-gov@nhs.net;
CTRU: stratcare-2-central-team-group@sheffield.ac.uk;
CTRU: ctru-saes-group@sheffield.ac.uk.

If a delegate is sending the form, the signing clinician (and PI if not the signee) should be copied in.

● SAE reports received overnight, at weekends, on public holidays or during University of Sheffield closure periods will be dealt with on the next working day.
● Receipt of the initial report will be confirmed within one working day by Sheffield CTRU

● Sites should contact the study team at CTRU stratcare-2-centralteam-group@sheffield.ac.uk if confirmation of receipt is not received within one working day.
● If no clinical assessment can be made immediately, it is recommended that the SAE form is sent to the CTRU and Sponsor regardless, and an assessment is obtained as soon as feasible on a new SAE form and forwarded to the CTRU in Sheffield and Sponsor.
● Follow-up or corrections to information should also be reported on a new SAE form and forwarded to the Sheffield CTRU and Sponsor as soon as possible.
● Sheffield CTRU will store completed SAE forms in the Trial Master File (TMF), will log all SAEs in the central SAE log and will reconcile records held against the trial database.

10.4 Adverse Device Effects and Device Deficiencies

It is not anticipated that adverse events, as defined in the StratCare trial, will be related to the use of the StratCare App. Consequently, there are no ADEs or SADEs expected for the trial.

Device deficiencies will be recorded on the 'Post-assessment' CRF, which is completed after the assessment process is complete.

10.5 Study specific exemptions

See causality, 10.3.2

10.6 CTRU responsibilities

- The Sponsor delegates to the CTRU responsibility for the reporting of SAEs to the research ethics committee.
- The CTRU will be responsible for reporting all SAEs to the Data Monitoring and Ethics Committee (DMEC) and Trial Steering Committee (TSC) via periodic safety reports during meetings. The Sponsor representative will receive notification of all SAEs via initial site notification and via the TSC data report.
- The CTRU will keep all investigators informed of any safety issues that arise during the course of the study.

10.7 SAE additional reporting

The DMEC and TSC will receive information on all AEs and SAEs, at a frequency agreed with each committee and documented in the appropriate charter/terms of reference.

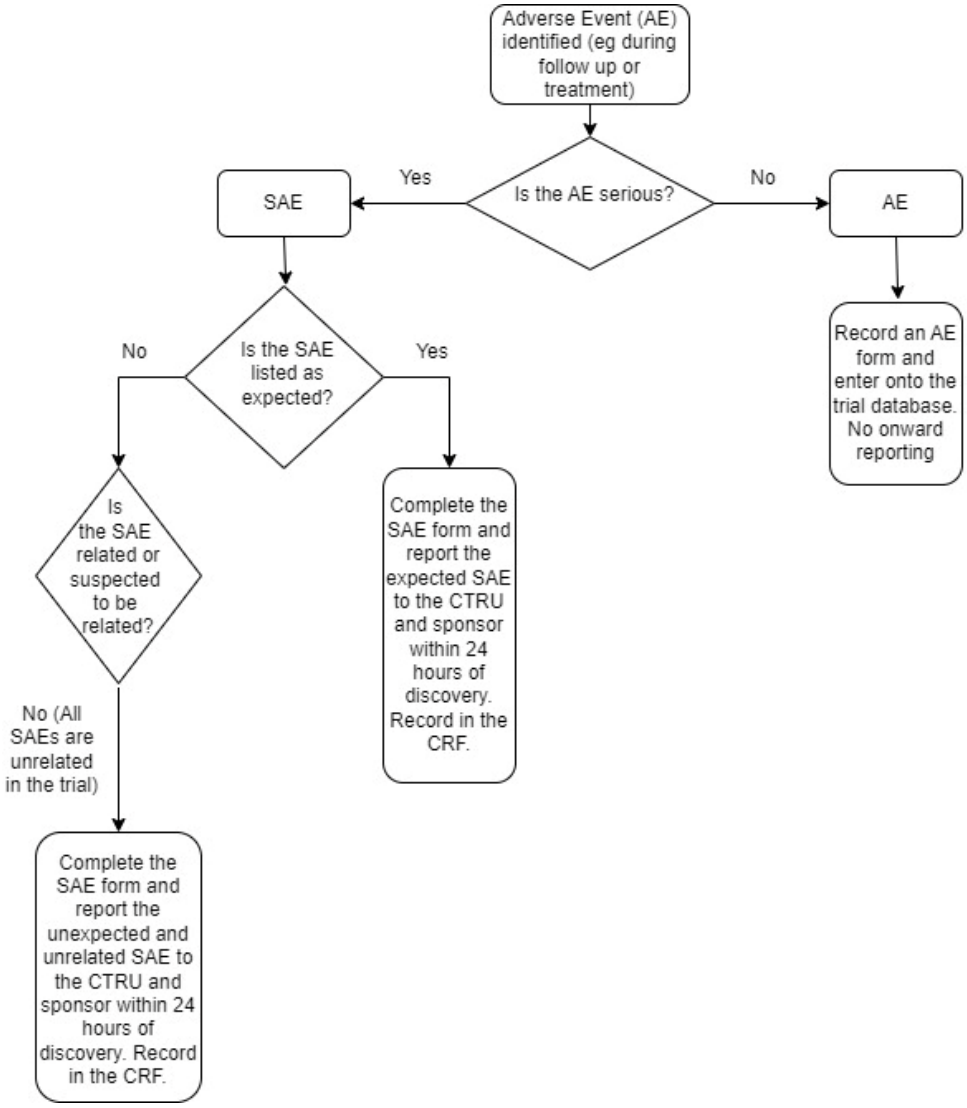


Figure 4: AE reporting procedure

11. Statistics

11.1 Sample size

Participants:
The primary outcome is the mean PHQ-9 score at 12 months. Data from our previous trial [13] reported a mean PHQ-9 score of 9.0 (SD 6.6) at follow-up, with a baseline and follow-up correlation of *r* = 0.46. Assuming a target difference of 2-points in the PHQ-9 score; a SD of 6.6, equivalent to a small standardised effect size of 0.30, a pre-post treatment correlation of 0.46 in the primary outcome measure and 90% power and 5% two-sided significance then for an individually randomised design 364 participants would be required.

Assuming a cluster size of **75 eligible** and consenting patients per Talking Therapies team, in the nine-month recruitment period, and an intra-class correlation coefficient (ICC) of 0.019 leads to design effect of **2.406** and a sample size of **876** participants across 12 Talking Therapies teams (clusters). Assuming 30% participant attrition, we would need to recruit **1252** patients across a minimum of 12 Talking Therapies teams (or approximately **104 patients**/team).

We propose to recruit 16 Talking Therapies teams to ensure the trial remains viable if up to four clusters (e.g., teams) drop out. A review of 86 cluster trials published in the NIHR Journal Library between 1997 and 2021 [29] found that the median number of clusters randomised (k = 44; IQR 25 to 74) was highly similar to the median number of clusters analysed (k = 43; IQR 25 to 69); showing that cluster dropout is not a common issue and it has less impact on sample power compared to participant attrition. In our previous trial [13] we were able to recruit 802 eligible participants across four Talking Therapies teams (~200 per team) in 5.4 months, with a minimal attrition rate of 4% (only 38 of cases had missing follow-up data). In our previous trial, none of the four services involved dropped out. Hence, we expect that 16 teams will enable us to recruit to the target sample (N=1252), even with a conservative expectation of 30% attrition, and with an available recruitment window of nine months. This target number of services is realistic to achieve based on our experience of research in this setting; however, adding and managing additional teams may be infeasible. A local audit suggests 13,040 patients are referred each year to one partner NHS Trust managing three Talking Therapies teams. From these, 6,000 per year would be eligible, of whom we estimate that 650/yr. would be willing to consent.

11.2 Statistical Analysis

The statistical analysis will follow intention-to-treat principles and CONSORT guidelines for Cluster RCTs [30] and it will be pre-registered with an international register for controlled trials. The unit of inference for the StratCare-2 RCT, i.e., the estimand of interest, is the effect of the intervention on a typical individual. Hence, we are interested in the 'participant-average treatment effect', which answers the question 'How effective is the intervention for the average participant?'

An estimand is a clear and explicit description of precisely what treatment effect is to be estimated in an RCT. It is made up of five connected elements: i) the population, ii) the treatments (you want to compare), iii) the outcome or endpoint, iv) how to account for intercurrent events and a v) population-level summary measures of how the outcome between the different treatment conditions will be compared.

Estimand attribute	Description
Population	Adult patients seeking and eligible for treatment for common mental health problems in Talking Therapies (formerly known as Improving Access to Psychological Therapies, IAPT) services.
Treatment(s)	StratCare App intervention used during initial assessment followed by any subsequent therapy/treatment (as needed) compared with participants randomised to usual care treatment group only (initial assessment as per usual, following stepped care principles) followed by any subsequent therapy/treatment (as needed)
Outcome (endpoint)	Mean total score on the PHQ-9, measured at 12 months post-enrolment.
Handling Intercurrent events that occur during the follow-up period.	1. Stopping randomised treatment for any reason – treatment policy (as part of treatment) 2. Switching treatments – treatment policy (as part of treatment) 3. Receiving treatment not randomised to, or not receiving randomised treatment - treatment policy (as part of treatment) 4. Use of other medications/treatments/therapy - treatment policy (as part of treatment) 5. Death – while alive (see note below)
Summary measures	Difference in mean PHQ-9 scores/outcomes between the two randomised groups

Table 4: Estimand framework applied to StratCare-2 CRCT

A treatment policy strategy to handle intercurrent events means *"regardless of any post randomisation events, the treatment effect is described from the final outcome measure in all patients. Note that this approach cannot be used for truncated events, for example, where a variable cannot be measured due to death"* [31].

The while alive policy to handle deaths as an intercurrent event implies that we are interested in the effect of treatment on outcome until death, and that we will include participants' data, in the analysis, until they die, and not included (or impute) any data thereafter [32].

11.2.1 Research questions answered by the estimand framework

In adults seeking treatment for common mental health problems using Talking Therapies services, what is the difference in mean 12-month post-enrolment PHQ-9 scores between participants randomised to the StratCare App intervention used during initial assessment followed by any subsequent therapy/treatment (as needed) compared with participants

randomised to USC treatment only (initial assessment as per usual, following stepped care principles) followed by any subsequent therapy/treatment (as needed) up to 12-months from baseline or death (whichever occurs first), regardless of study treatment discontinuation, for the average participant?

11.2.2 Primary statistical analysis

The primary outcome (mean PHQ-9 score at 12 months post-enrolment) will be compared between the randomised groups using a marginal or population averaged linear regression model, with coefficients estimated by Generalized Estimating Equations (GEE), with robust (Huber/White) standard errors and an exchangeable within-group (Talking therapies team cluster) correlation and baseline PHQ-9 score and randomised group as covariates.[33, 44] The adjusted regression coefficient estimates for the randomised group parameter along with its 95% confidence interval (CI) from the model will then be reported.

11.2.3 Missing primary outcome data

For the primary outcome, PHQ-9 score at 12 months post-enrolment, missing data will be imputed through a variety of methods, including multiple regression [33] and multiple imputation using chained equations (MICE) using imputation models that where possible acknowledge the clustered structure of the data, or other appropriate methods if data are not missing at random. The estimates of the treatment effect and its associated confidence interval, from the various imputation methods, will be graphically displayed alongside the results for the observed data.

11.2.4 Other sensitivity analyses for the primary outcome

The analysis of the primary outcome will be repeated with additional potential prognostic participant-level covariates such as ethnicity and level of deprivation (IMD score of the postcode where the participant resides). The estimates of the treatment effect and its associated confidence interval, from the model, will again be graphically displayed alongside the results for the primary statistical analysis described above. Other sensitivity analyses for the primary outcome will include using different within cluster correlation structures such as unstructured or independent in the marginal or population-averaged linear regression model.

In order to aid comparability with our prior trial [13], we will repeat the above analysis, of the 12-month PHQ-9 outcome, using a marginal or population-averaged logistic regression model, with coefficients estimated by GEE, and with robust standard errors and an exchangeable within-cluster correlation and baseline PHQ-9 score and randomised group as covariates, and a binary outcome for whether or not a participant meets the criteria for remission of symptoms (reliable and clinically significant improvement or RCSI). For the PHQ-9 outcome this will be defined as post-enrolment 12-month scores <10 and improved by >= 6 points compared to baseline. The proportion of cases meeting criteria for remission will be reported for the intervention and the control groups, as well as the odds ratios and their associated 95% CI from the population averaged model.

The main analysis of the StratCare-2 trial will be the ITT analysis (analysis 1 in Figure 5). A series of sensitivity analyses for the primary outcome, the PHQ-9 score at 12 months will also be conducted as shown in Figure 5. These will include Analysis 2 – which is broadly equivalent to a per-protocol analysis and will only include patients in the StratCare arm whose treatment decision matched the StratCare recommendation. This secondary analysis enables us to assess the outcomes of stratified care if it were followed consistently in every case. A third level of analysis will involve principal stratification and Complier-average causal effect (CACE) analysis. For this analysis a “complier” in the StratCare arm will be defined as a patient whose

treatment decision matched the StratCare recommendation AND who received four or more sessions of therapy.

CACE analysis will use the randomised treatment allocation (exogenous or instrumental variable) and covariates (e.g. age, sex and baseline PHQ-9 score) to predict treatment receipt/compliance (endogenous), before using this prediction in place of treatment in the primary analysis model. CACE analysis will use a two-stage least squares regression with age, gender, and baseline PHQ-9 scores as covariates and robust standard errors (at each of the two stages) that allow for the clustering by Talking Therapy team. The CACE sensitivity analysis aims to yield estimates of the effects of the StratCare intervention for individuals who complied with treatment.

StratCare-2 Analyses

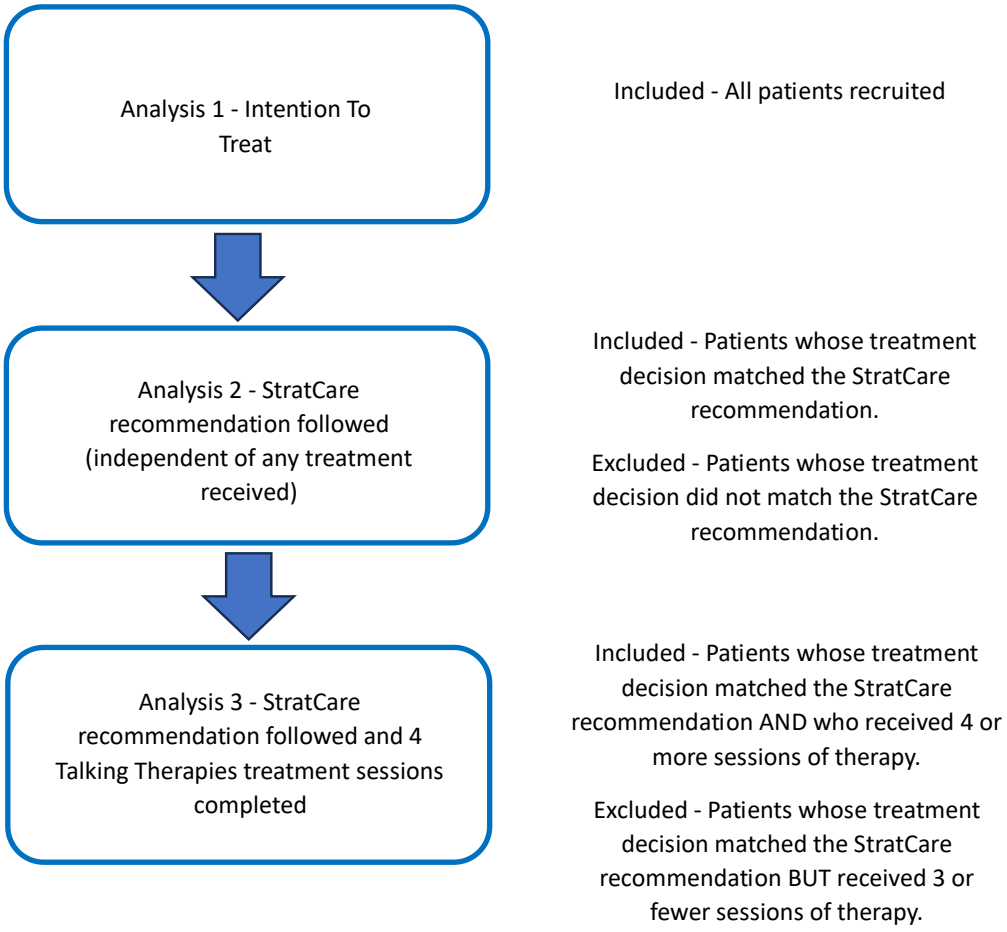


Figure 5. StratCare 2 Sensitivity Analyses

11.2.5 Analysis of secondary outcomes

The primary outcome the PHQ-9 will also be measured at six- and 18-months post-enrolment (in additional to the primary endpoint/time point of 12 months). Other continuous secondary patient-reported outcomes such as the GAD-7, ReQoL-10, EQ-5D will be measured at six, 12- and 18-months post-enrolment. For each secondary outcome we will estimate the treatment effect at each post-enrolment follow-up time point using a marginal or population averaged linear regression model, with coefficients estimated by GEE, with robust standard errors and

an exchangeable within-cluster correlation and baseline score and randomised group as covariates. The adjusted regression coefficient estimates for the randomised group parameter along with its 95% confidence interval (CI) will then be reported from the model.
Again, in order to aid comparability with our prior trial [13] we shall also analyse two further binary outcomes, at 12 months post-enrolment;
1) GAD-7 anxiety RCSI outcome the number of cases meeting criteria for remission of symptoms (reliable and clinically significant improvement or RCSI).
2) Talking Therapies reliable recovery, a binary outcome referred to as "recovery" which is used by Talking Therapies services [15].

A reliable recovery requires patients with case-level PHQ-9 and/or GAD-7 symptoms to have (1) attained statistically reliable improvement on case-level measures, (2) to have subclinical symptoms on both measures after treatment, and (3) to not have statistically reliable deterioration on any of these measures after treatment.

Again, a marginal or population-averaged logistic regression model, with coefficients estimated by GEE with robust standard errors and an exchangeable within-cluster correlation and baseline score and randomised group as covariates will be used. The proportion of cases meeting criteria for remission will be reported in the intervention and the control groups, as well as the odds ratios and their associated 95% CI from the population averaged model.

11.2.6 Adverse events

These will be based on serious adverse events (SAE) case report forms. A serious adverse event is defined as any adverse event or adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. The following summaries will be presented: the number and percentages of patients reported as having Serious Adverse Events (SAE) in each treatment arm; the number and percentages recorded as having all forms of Adverse Events (AE) in each arm; this will be presented as overall and stratified by AE classification.

11.2.7 Exploratory Analyses

An exploratory analysis using a mixed-effects linear regression model with the primary outcome (PHQ-9) at 12-months post-enrolment as the response will be carried out. We will use an interaction statistical test between the randomised intervention group and subgroup to directly examine the strength of evidence for the treatment difference between the treatment groups (Intervention versus usual care) varying between subgroups. Complex case (yes or no, ethnicity, deprivation (standard case)) will be the only a priori defined subgroups to be considered for interaction test. Exploratory analysis will be performed regardless of the statistical significance on the overall intervention effect.

Further details will be provided in the study Statistical Analysis Plan. This will be finalised before data collection is completed.

12. Sub-studies

12.1 Qualitative Sub-Study

12.1.1 Selection of qualitative participants

Participants will be individuals who have been recruited to the StratCare-2 trial and completed the initial assessment. Participants will be recruited from both arms of the trial.

A purposive sampling strategy will ensure to recruit a socioeconomically and culturally diverse sample of participants for interviews. Potential participants will be approached by the qualitative researcher by email or telephone after the initial assessment has been completed. The researcher will make clear at this approach that participation is optional. Views will be sought at various timepoints throughout the treatment process (pre-treatment, during treatment, post-treatment) to explore whether views vary across this period.

Participating assessing clinicians will be clinicians who have completed at least one assessment as part of the trial. Clinicians will be approached by the qualitative researcher by email and asked if they would like to participate in the interview. If they express an interest in participating in the qualitative interview then the qualitative researcher will provide them with the relevant PIS, and discuss this with them via telephone or email, depending on clinician preference. The interview will be described to them and clinicians will be given the opportunity to ask any questions or discuss any concerns. They will then be given as long as they feel is needed to consider the information prior to making a decision about whether they would like to take part.

12.1.2 Consent

Consent for trial participants to be contacted for the qualitative study will be received as part of the main trial consent process. Participants will be approached by the qualitative researcher by telephone or email and asked if they would like to participate in the interview. If they express an interest in participating in the qualitative interview then the qualitative researcher will provide them with the relevant PIS, and discuss this with them via telephone, videocall or email, depending on participant preference. The interview will be described to them and participants will be given the opportunity to ask any questions or discuss any concerns. Consent will be received verbally during approach and verbal consent will be audio recorded by the qualitative researcher prior to the interview.

Trial assessing clinicians will be asked to provide fully informed verbal consent prior to the interview. Socio-demographic data collected at approach will include age and job role (e.g., PWP, psychotherapist, counsellor etc). Additional socio-demographic data collected for all those study clinicians who meet eligibility criteria and provide consent will include: self-identified gender, ethnicity, full postcode, current occupation, number of years since qualifying as a clinician, banding, highest level of qualification.

12.2 Qualitative Data Collection

Semi-structured interviews with a purposive sample of clinicians and patients who took part in the trial will be conducted by a) a research assistant, trained and supervised by an expert qualitative researcher, or b) the qualitative researcher, to carry out a process evaluation investigating implementation barriers, enablers, and factors affecting adherence to the AI-driven stratified care model. This will focus on aspects of “explainable” and “ethical” use of AI: (a) whether patients understand and accept AI-driven recommendations, and (b)

whether there are situations where algorithmic recommendations are deemed clinically inappropriate by clinicians. Qualitative interviews will also capture information about patients' and clinicians' experiences of the shared decision-making process.

Interviews will be conducted face-to-face, via telephone or by videoconferencing, determined by participant preference, and will be recorded using an encrypted Dictaphone or through the video conferencing platform. Recordings will be removed from the device as soon as possible and stored on the University of Sheffield secure server. Interviews will be anonymised and transcribed verbatim for analysis.

Transcripts of interviews will be analysed by the qualitative researcher using framework analysis [34]. This will be informed by Sekhon's acceptability of healthcare interventions framework [35] and *Normalisation Process Theory* [36], which can help identify whether interventions are likely to become embedded and integrated as part of routine practice or not [37]. PPIE members will be invited to participate in the analysis of the collected data and training will be provided by the qualitative lead as appropriate prior to analysis.

12.3 Health Economic Analysis

An economic analysis will be conducted from the NHS and Personal Social Services perspective over the 18-month study time-horizon. A cost-utility analysis will use quality-adjusted life years (QALYs derived from the EQ-5D questionnaire, and tariff based on the UK public value set) as the measure of quality of life. Health and social services resource use will be valued using NHS reference costs and the personal and social services resource use database[38]. Regression analysis will control for baseline utility[39]. We will estimate the incremental cost effectiveness ratio for stratified care compared to a USC pathway, using bootstrapping to estimate confidence intervals [40].

Probabilistic sensitivity analysis will help understand uncertainty in cost-effectiveness estimates. Decision uncertainty will be presented on a cost-effectiveness acceptability curve [41]. Additional sensitivity analyses will be conducted for resource use and unit costs. Controlling for baseline cost in the regression analysis will be explored in a sensitivity analysis. Scenario analyses will explore alternative costing perspectives; that is, NHS and NHS/PSS perspectives. Results of the cost-effectiveness analysis will be reported in line with the Consolidated Health Economic Evaluation Reporting Standards 2022 [42] Statement.

12.4 Process Evaluation

We will collect fully pseudonymised clinical pathway and outcomes data for all participating patients. These data sources will be retrieved from electronic health records, deidentified, and structured in a way that will enable us to characterise the full treatment pathway for patients. It will include information on what treatments were accessed, how long the treatments lasted, whether or not patients completed or dropped out of treatment. This will enable us to examine aspects of the logic model, such as whether patients did indeed accept, start and complete their recommended interventions.

Both quantitative (e.g., anonymised electronic health records data) and qualitative data will be used to undertake a thorough process evaluation of the logic model. Data on reach, dose and fidelity will be reported alongside qualitative findings on implementation, following guidelines for the process evaluation of complex interventions [34].

As the assessments for these studies are integrated into the procedures for the main study, the details are included throughout the protocol and in study-specific guidance where necessary.

12.5 Evaluation of Generalisability

As StratCare-2 is embedded within each participating NHS Talking Therapies service where they all collect the nationally mandated outcome measures at each attended therapy session, we will design a direct test of the generalisability of results obtained by trial participants with the wider population of attendees at these services. The crucial question addressed is whether trial participants, patients and practitioners, are representative of those within each of the participating services/teams. This question is central to address the perceived gap between results from trials and those derived from routine practice.

In addition to the outcome measures taken at each session, the NHS Talking Therapies programme routinely collects information on patient demographics and presenting issues, including data that can be transformed into the Index of Multiple Deprivation. We will seek permission to download this data for each participating service/team for the time period two years preceding the start of each service/ teams' participation until the discharge of the final participant at a service/team. In some services, we expect the waiting time may be lengthy (e.g., 9-12 months), therefore a two-year data collection period would enable us to capture outcome data for cases with lengthy waiting times. This procedure comprises some of the features of a trial within a cohort study (TWICs [43]), namely accessing the pre-existing mandated outcome measurement but, in effect, is sampling the cohort around the trial whereas a TWIC design adopts the existing cohort within which to embedded and conduct multiple RCTs.

From each team, the data collected will include demographics (age, gender, ethnicity, employment status, index of multiple deprivation, self-reported disabilities) and clinical care data (diagnoses, number of therapy sessions, types of treatments offered, reason for discharge, last step accessed in stepped care system, item level data for PHQ-9, GAD-7 and WSAS).

13. Trial supervision

The study will be conducted in line with the Helsinki Declaration. RDaSH is the nominated sponsor. Research governance will be led by the RDaSH Grounded Research Team, the Research and Development Organisation of the lead Trust. The local Principal Investigator (PI) will be responsible for the trial at each participating site, and it will be registered and approved with each local R&D department.
The study will be conducted in accordance with the protocol, ICH-GCP and Sheffield CTRU SOPs. The three committees which will govern the conduct of the trial are:

- Trial Steering Committee (TSC)
- Data Monitoring and Ethics Committee (DMEC)
- Trial Management Group (TMG)

13.1 Trial Steering Committee

The TSC will oversee the trial and meet twice yearly, as defined by its terms of reference. It will be Chaired by an independent expert academic (to be appointed). The TSC will comprise individuals who are experts in their field and who collectively possess a range of relevant skills and an interest in the trial but who are not directly involved with the trial. This will include an independent statistician, an independent health economist and a PPIE member with lived experience of mental health problems. Representatives of the sponsor will also be invited to attend meetings. The role of the TSC will be to provide advice on all aspects of the trial and overall supervision with respect to progress, relevant approvals, protocol

adherence, patient safety, as well as agree proposals for substantial amendments. It will also consider recommendations from the DMEC.

13.2 Data Monitoring and Ethics Committee

The DMEC will regularly review reports on the accumulating data and provide feedback to the TSC. The DMEC will meet twice a year to ensure that the trial is progressing appropriately, and that safety is maintained at all times. The DMEC will be chaired by an independent expert academic (to be appointed) and will include at least three independent members with relevant clinical and statistical expertise. The DMEC will have access to all data, including blinded data. The DMEC may recommend to the TSC or funder that the trial is stopped or modified on the basis of data / on safety grounds.

13.3 Trial Management Group

The TMG will comprise the Chief Investigator, co-applicants, collaborators and relevant trial staff. If specific expertise is required for an issue, additional invitees will be allowed to attend with the agreement of the group. The TMG will meet in person/via teleconference approximately every month initially until recruitment is well established and then every two-three months or as agreed throughout the remainder of the trial. It has been agreed that the PPIE co-applicant will meet separately and feed back into the group. This group will set target deadlines, monitor the conduct and progress of the trial, and troubleshoot any issues that arise. It will also review recruitment figures, Adverse Events, research incidents and substantial amendments to the protocol prior to submission to the Research Ethics Committee. In addition, it will ensure adherence to Data Protection Act, ethical guidelines, Information Governance procedures, and other relevant guidance. The TMG will send updates to the TSC and DMEC. The Chief Investigator, the trial manager and research assistant will maintain monthly contact with recruiting sites via site visits and telephone or video calls to ensure that recruitment targets are met and any issues with recruitment are managed promptly. “Trial champions” will be identified at each of the sites so that knowledge and processes about the trial are disseminated to all clinicians likely to be involved, and not just the PIs at each site.

14. Data handling and record keeping

14.1 Data Management

The Sheffield CTRU will oversee data collection, management and analysis and ensure the trial is undertaken according to Good Clinical Practice Guidelines and CTRU SOPs. Data will be collected and retained in accordance with the Data Protection Act 2018 [44].

RedCap may be used as digital option to collect primary and secondary outcome measures (see section 7). Digital versions of outcome measures will be sent via an online link to participants, managed by site staff members and the central research team at RDaSH and the CTRU. Access to the RedCap system is restricted to authorised individuals via a personalised login. StratCare RedCap operates on secure, access-restricted servers hosted by Corporate Information and Computing Services (CiCS) at the University of Sheffield. RedCap demonstrates conformity to GDPR.

Qualtrics may be used as digital option to collect primary and secondary outcome measures (see section 7). Digital versions of outcome measures will be sent via an online link to participants, managed by site staff members and the central research team at RDaSH and the CTRU. Access to the Qualtrics system is restricted to authorised individuals via a personalised login. Qualtrics servers are protected by high-end firewall systems and scans

are performed regularly by Qualtrics to ensure that any vulnerabilities are quickly found and patched. Qualtrics has obtained ISO 27001, ISO/IEC 27017, ISO/IEC 27018 and ISO 9001 security certifications: these are internationally recognised best practice frameworks for information security management systems.

The StratCare App is developed and supplied by MindLife, a UK-based digital technology company. MindLife are NHS Data Security and Protection Toolkit compliant (Registration YGMYK). All data stored in the App is anonymised, and stored on a secure, encrypted UK-based cloud database. Data will be transferred to the University of Sheffield using a secure, encrypted data transfer system, and stored on the University of Sheffield secure, access-restricted server. No personally identifiable data is stored in the App.

PCMIS provide Electronic Patient Health Record services to some NHS Talking Therapies services. Where this applies to StratCare-2 research sites, periodic downloads of patient record summaries for trial patients will be provided by PCMIS. Data will be transferred up to bi-monthly during data collection to the University of Sheffield using a secure, encrypted data transfer system. Data received in this manner will be stored on the University of Sheffield secure, access-restricted server.

Trial data may be entered on a study database hosted on CTRU's web-based data management system (Prospect). Prospect stores all data in a PostgreSQL database on virtual servers hosted by Corporate Information and Computing Services (CiCS) at the University of Sheffield. Prospect uses industry standard techniques to provide security, including password authentication and encryption using SSL/TLS. Access to Prospect is controlled by usernames and passwords, and a comprehensive privilege management feature can be used to ensure that users have access to only the minimum amount of data required to complete their tasks. This will be used to restrict access to personal identifiable data.

The research staff at sites will be responsible for data entry locally. The Sheffield CTRU trial team will work with sites to ensure the quality of data provided. The trial manager, research assistant, data manager, PIs, any trial staff at RDaSH and site staff will be able to access the database via a web browser through the use of usernames and encrypted passwords. The system has a full electronic audit trail and is regularly backed up. The study database will incorporate quality control procedures to validate the trial data. Error reports will be generated where data clarification is needed. Output for analysis will be generated in a format and at intervals to be agreed between Sheffield CTRU and the Chief Investigator. Study-specific procedures for data management will be detailed in a data management plan.

14.2 Completing CRFs

All CRFs will be completed electronically by staff that are listed on the site staff delegation log and authorised by the Chief Investigator/Principal Investigator to perform this duty. The Principal Investigator will be responsible for the accuracy of all data reported in the CRF. In line with RSaSH's (Sponsor) Data Protection Policy, study documentation and anonymous data will be securely kept for a period of 10 years following completion of the study.

14.3 Data handling

All data will be collected in accordance with the patient information sheets for participants and study clinicians and this protocol. RDaSH, as the study sponsor, will act as the data controller for the study. All data will be handled in accordance with The Data Protection Act 2018. Data management will be provided by the University of Sheffield CTRU who adhere to their own SOPs relating to all aspects of data management including data protection and

archiving. A separate data management plan (DMP) will detail data management activities for the trial in accordance with the CTRU's Data Management Plan SOP

Participants will be assigned unique identification numbers. RedCap or Prospect will store a participant's name, address, phone number and email address, which will be retrieved from clinical records. RedCap or Prospect's permissions system will be used to ensure that access to names and contact details will be restricted to those members of the study team who need to contact participants. All data will be held on a secure server with access restricted to the research team.

Audio files of qualitative interviews will be recorded on encrypted digital voice recorders and will be stored on the University of Sheffield secure, access-restricted server. All data on encrypted digital voice recorders will be deleted after the data have been transferred.

Data will not be transferred to any party not identified in this protocol and will not be processed and/or transferred other than in accordance with the patients' / clinician's consent.

14.4 Confidentiality

Participant confidentiality will be respected at all times. All data will be handled in accordance with the UK's Data Protection Act (2018) [44]. The CRFs will not bear the participant's name or other personal identifiable data. The participant's trial identification number will be used for identification, and this will be clearly explained in the information sheets. All participant information will be stored in accordance with the UK's Data Protection Act (2018), with any personally identifiable physical information stored in locked cabinets. Each participant will be assigned an identification code, which will be used in all data storage, and will not contain any names or other personally identifiable information.

Participants will be assured that confidentiality will be kept unless there is evidence of risk of harm to self or others. This will be specified in the information sheet.

14.5 Archiving

Data held by the CTRU will be stored in accordance with the archiving Standard Operating Procedure (*SOP PM012 Archiving*). Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for the period stated above.

14.6 Data Sharing

Open sharing of trial data encourages and supports research transparency. Data acquired in clinical trials also has the potential to answer questions outside the scope of the original research, and additional patient benefit may be gleaned when data is shared appropriately with others.

In line with the NIHR position on the sharing of research data [45], StratCare-2 will share its data using a controlled access, data repository approach. After the closure of the trial, simplified, minimised, anonymised datasets will be made available within a recognised data repository. This will be within a 'controlled access system' (i.e. data access requires approval and compliance with a formal data sharing agreement), in line with UKCRN recommendations [46]. A controlled access approach is recommended, as supported by the Medical Research Council (MRC) Hubs for Trials Methodology Research (HTMR) guidance and the UKCRC [46,47].

A study-specific Data Sharing Plan will be agreed and approved by the sponsor, TMG, TSC and CTRU Quality Assurance team prior to any data being deposited or shared. This will outline where data is stored, what is stored, and how access to it is requested, reviewed and approved.

15. Data access and quality assurance

15.1 Site assessment

Throughout this protocol, the trial 'site' refers to the NHS Trust at which trial-related activities are conducted. Participating sites must be able to comply with: Trial procedures, clinical care, adverse event reporting, follow-up schedules and all requirements of the trial protocol. There may be more than one Talking Therapies Team participating in StratCare-2 at each site.

All site staff, including research staff, must be appropriately qualified by education, training and experience to perform the trial-related duties allocated to them, which must be recorded on the site delegation log. Principal Investigators must hold GCP. The trial team will provide study Clinicians with bespoke GCP training to cover the fundamental principles required for the trial. The study team will be provided with CVs for all staff which must be kept up to date, and copies held in the Investigator Site File (ISF), and the Trial Master File (TMF).

Before each site is activated, capacity and capability to conduct the trial will be assessed and documented. The CTRU will arrange a site initiation visit with each site or carry this out remotely. Site staff will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked. Once all the required documentation is in order (including contracting), confirmation of capacity and capability has been received and site staff have been trained, CTRU will formally activate the site to start recruitment. Sites should not open to recruitment until CTRU have provided this confirmation of activation.

15.2 Risk assessment

A risk assessment has been performed by the CTRU, in accordance with Sheffield CTRU Standard Operating Procedures.

Central- and on-site monitoring will be undertaken at a level appropriate to the detailed risk assessment, as agreed with the sponsor, and will be documented in the Site Monitoring Plan (SMP, see 15.4).

15.3 Reporting serious breaches and non-compliances

A "serious breach" is a breach of either: the conditions and principles of GCP in connection with the trial or the protocol relating to the trial, which is likely to effect to a significant degree –

the safety or physical or mental integrity of the participants of the trial; or
the scientific value of the trial.

The sponsor will be notified immediately of any case where the above definition may apply during the trial conduct phase. The sponsor of a clinical trial will notify the REC in writing within seven days of becoming aware of a serious breach.

All serious breaches and protocol non-compliances should be reported to CTRU within 24 hours of site staff becoming aware. A study-specific non-compliance standard operating procedure will be followed for the trial.

15.4 Site monitoring

The sponsor will determine the appropriate level and nature of monitoring required for the trial based on the risk assessment. Risk will be assessed on an ongoing basis and adjustments will be made accordingly. The degree of monitoring will be proportionate to the risks associated with the trial. A trial-specific site monitoring plan will be established prior to the commencement of the trial, with agreement of the sponsor. The trial will be monitored in accordance with the agreed plan. The Sheffield CTRU SOPs will be followed.

15.5 Central monitoring

CTRU staff will review entered data for possible errors and missing data points.

16. Publication

A Plain English summary of the trial results will be sent to all participants and clinicians involved.

Results of the study will be disseminated through peer-reviewed scientific journals and at clinical and academic conferences, as well as submission of a final report to the funder, which will be made available online.

Details of the study will also be made available on the trial website and the Sheffield CTRU website. Summaries of the research will be updated periodically to inform readers of ongoing progress.

The results will be published on a freely accessible database within one year of completion of the trial.

Full details, including guidance on authorship, are documented in the Publication and Dissemination Plan.

17. Finance

The research costs for the study have been funded by the NIHR HTA programme (HTA 153364; £1,563,070.43; 25th September 2023).

18. Ethics approval and regulatory compliance

The London, Brighton & Sussex Research Ethics Committee has approved the trial.

Before initiation of the study at participating sites, the protocol, consent process documents and information materials to be given to the participants will be submitted to London, Brighton & Sussex Research Ethics Committee. Any further amendments will be submitted and approved by the HRA and ethics committee.

The study local information pack will be submitted to local participating Trusts to confirm Capacity and Capability before any research activity takes place.

Amendments will not be implemented prior to receipt of the required approvals. Before any NHS site may be opened to recruit participants, the Sponsor and Sheffield CTRU must receive confirmation of capability and capacity in writing from the relevant Trust's Research & Development department. It is the responsibility of the Principal Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approvals, including NHS Permission (where required) at the site. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual participants. An annual progress report will be submitted to the Research Ethics Committee 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 prepare the annual progress report. Within 90 days after the end of the trial, the Chief Investigator/Sponsor will ensure that the main Research Ethics Committee is notified that the study has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial. The Chief Investigator will supply the Sponsor with a summary report of the trial, which will then be submitted to the Research Ethics Committee within one year after the end of the trial.

19. Sponsor and site approval

Before initiation of the study at participating sites, the protocol, informed consent forms, and information materials to be given to the participants will require sponsor approval.

A site agreement between the Sponsor, participating sites and Sheffield CTRU outlines responsibilities of all parties and is to be signed prior to commencement of recruitment at sites.

Recruitment of study participants will not commence at a site until a letter of of Confirmation of Capacity and Capability (CCC) has been issued by the site, and Green Light has been issued by the sponsor.

20. Trial organisation and responsibilities

20.1 Principal investigators

Each site will have a local Principal Investigator (PI) who will be delegated responsibility for the conduct of research at their centre and must sign a declaration to acknowledge these responsibilities. The local PI should ensure that all relevant staff involved are well informed about the trial and trained in study procedures, including obtaining informed consent and conduct of the trial according to GCP. The local PI will liaise with the Trial Manager on logistic and administrative matters connected with the trial.

20.2 Sheffield Clinical Trials Research Unit (CTRU)

The Sheffield CTRU at the University of Sheffield will provide set-up and monitoring of the trial conduct to CTRU SOPs and the GCP conditions and principles as detailed in the UK Policy Framework for Health and Social Care Research 2023 [48] . CTRU responsibilities include randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support the main REC, HRA and site-specific submissions, clinical set-up, on-going management including training, monitoring reports and promotion of the trial.

The CTRU Study Manager will be responsible for supplying investigator site files to each collaborating centre after relevant ethics committee approval and local R&D Confirmation of Capacity and Capability (CCC) has been obtained. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses. The CTRU will develop the site monitoring plan and data management plan and will assist the CI to resolve any local problems that may be encountered during the trial including any issues of noncompliance.

21. Patient and public involvement and engagement (PPIE)

21.1 PPIE

The following patient and public involvement and engagement is planned:

- We will recruit a PPIE group specific to the trial via the trial team networks.
- The trial team includes a PPIE co-applicant, who will sit on the Trial Management Group.
- We will invite interested members of our PPIE group to join our Trial Steering Committee. We plan to recruit two members to the TSC.
- The PPIE group will be involved in the development of the protocol, interview topic guide and patient materials (e.g., participant information sheets and videos).
- We will invite interested members of our PPIE group to help us to produce training materials for clinicians (e.g., videos exemplifying an assessment process using the StratCare App and model), with training and support from the PPIE co-leads.
- Where interested, we will invite PPIE members to undertake the qualitative analysis, with training and support. We will discuss the qualitative findings and the process evaluation findings with the PPIE group to aid interpretation. PPIE group members will be asked to comment on the main results prior to publication.
- We will invite interested members of our PPIE group to participate in local and national presentations and co-write blogs for a public audience with us about our key findings (with training and support from the PPIE co-leads).

To ensure genuine, consistent partnership with patients and the public, two experienced PPIE Co-Leads will lead all PPIE input. The PPIE co-leads will conduct all the activities described in NIHR guidance (e.g., setting and refining the PPIE strategy as the project progresses). We will run regular PPIE groups of up to 12 participants, comprising adult volunteers with lived experience of mental health problems and Talking Therapies services. It is anticipated that people with diverse socio-demographic characteristics will be included to represent a variety of perspectives. Over the course of the project, PPIE group members will meet both separately and jointly, to input into research design, aspects of delivery, interpretation of the data and dissemination of the research findings. Examples of how we expect to work with the PPIE group include asking participants to advise on the content of any project information and training materials to ensure these are clear and accessible and to provide insight into the acceptability of the research and treatment burden, possible barriers to access and adherence and how to address them. We will invite interested members of our PPIE group to participate in local and national presentations and co-write blogs for a public audience with us about our key findings. We will support the PPIE group's involvement in the qualitative work and the process evaluation. Throughout the project we will liaise with Sheffield Deep End PPIE panel [49] (situated within Sheffield's most marginalised communities) to ensure acceptability of the trial process and information for diverse groups, and to explore solutions to identified barriers.

We will follow INVOLVE guidance [50] and adhere to standards published by the NIHR Centre for Engagement and Dissemination [51]. GRIPP2 guidance will be followed to ensure best practice in the evaluation, monitoring and reporting of PPIE [52].

21.2 Other stakeholders

Talking Therapies service managers and practitioners are also key stakeholders for this project. We will convene a separate clinical advisory group with qualified psychological wellbeing practitioners and service managers, to be able to discuss technical and clinical issues relating to the StratCare App and related training materials and clinical protocols; and to support implementation and monitoring within clinical services.

22. Indemnity / compensation / insurance

The University of Sheffield has in place clinical trials insurance against liabilities for which it may be legally liable, and this cover includes any such liabilities arising out of this clinical study.

Standard NHS indemnity operates in respect of the clinical treatment that is provided.

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Appendices

1. Exclusion criteria from Talking Therapies services

- Patients with sub-clinical depression symptoms (PHQ-9 < 10).
- Patients who are acutely suicidal (thoughts of suicide with a clear plan or intent to act on them) at the time of initial assessments, and who require referral to crisis services.
- Patients with severe mental disorders ineligible for treatment in IAPT (e.g., psychosis, bipolar disorder).
- Patients with substance use disorders requiring referral to addiction treatment services.
- Patients with profound intellectual disabilities.
- Not meeting criteria for a common mental disorder, in accordance with the NHS Talking Therapies Manual