RESEARCH PROTOCOL
A pilot cluster randomised controlled trial of psychological treatment selection for depression

Short title of study	
TherapyMatch-D	
Protocol version and date	**Research Ethics Committee (REC) reference**
(v2.3) 18th July 2024	23/LO/0487
Sponsor organisation	**Controlled trials registration number**
Rotherham Doncaster and South Humber NHS Foundation Trust	ISRCTN21721966

Research team

Paulina Gonzalez Salas Duhne[1,2], Jaime Delgadillo[2], Michael Barkham[2], David Saxon[2]
1 – Grounded Research Team, Doncaster and South Humber NHS Foundation Trust, UK
2 – Clinical and Applied Psychology Unit, Department of Psychology, The University of Sheffield, UK

Principal investigator contacts details

Paulina Gonzalez Salas Duhne
Grounded Research, 2 St Catherine's Close, Tickhill Road Hospital, Balby, Doncaster DN4 8QNTel: 03000 212456; Email: p.gonzalez1@nhs.net

Contents of the study protocol

1. Synopsis of the study	
Short study title	TherapyMatch-D
ISRCTN registration no.	21721966
Study Design	Pragmatic pilot multi-site cluster randomised controlled trial of a psychological treatment selection model versus allocation as usual in adults with depression in primary mental health
Setting	Talking Therapies from NHS Trusts and Non-NHS sites
Study Participants	Patients who access routine psychological treatment for depression in primary mental health services and are suitable for high intensity psychological therapies.
Primary Objective	To pilot the effectiveness of an artificial intelligence (AI) treatment selection model to improve clinical outcomes (i.e., reduce depression) in adults accessing two high intensity psychological therapies: Cognitive Behavioural Therapy (CBT) and Person-Centred Experiential-Counselling for Depression (PCE-CfD), relative to allocation to these two therapies as usual (AAU).
Secondary Objectives	To evaluate the feasibility and effects of an AI treatment selection model for depression to improve clinical outcomes. Specifically, to improve: ▪ Feasibility: adherence to AI treatment selection recommendation, outcome expectancy ▪ Secondary effects: anxiety and functional impairment symptoms, drop-out rates and adverse events
Primary outcome(s)	Reliable and Clinically Significant Improvement in depression using a patient-level measure (PHQ-9).
Randomisation and interventions	Consenting Talking Therapies sites will be randomly assigned to an intervention group labelled '*TherapyMatch-D'* or a control group labelled 'allocation as usual' (AAU). Consenting therapists of sites in both groups will be trained to use a computer programme called *TherapyMatch-D* containing an algorithm which will identify consenting patients with a differential treatment response (prior research suggests would be approx. 30% of the sample). From that sub-sample, patients in *TherapyMatch-D* group will be provided a personalised treatment selection recommendation (between CBT and PCE-CfD) based on the targeted prescription algorithm to be used alongside shared decision making. Patients in AAU group will be allocated to treatment as usual (treatment selection based solely on shared-decision making). All patients without an identified differential treatment response across both groups (estimated to be approx. 70%) will also be allocated as usual to treatment (i.e., either CBT or PCE-CfD).
Planned Sample Size	Pilot trials do not require a formal sample size calculation. However, we will aim to recruit 6-10 clusters (3-5 sites randomised in each arm) with a total of 432 patients screened (216 patients per arm). As we expect approximately 30% of patients to have a differential response, we estimate there would be 128 eligible patients (64 patients per arm).
Data analysis method	1. Trial data will be summarised using a CONSORT diagram and analyses will be based on *intention-to-treat* principles. 2. Patient-outcome data will be analysed using multi-level logistic regression. Post-treatment reliable and clinically significant improvement

	(RCSI) in depression symptoms will be the primary outcome, and will be compared between TherapyMatch-D and AAU. 3. The primary aim will be to examine between-group differences comparing cases using the treatment selection model versus AAU, in the sample of patients where a differential treatment response was identified. 4. Secondary analyses will involve comparing between-group differences in anxiety symptoms, functional impairment, dropout rates, and outcome expectancy, and adverse events.
Study Period	36 months (2-year active study period, plus 12 months analyses and dissemination)

2. Background and rationale

Depression is one of the most common mental health disorders globally and the leading cause of disability (WHO, 2017). National guidelines for the treatment of severe, complex, or persistent depression in adults (NICE, 2021) recommend high intensity psychological therapies; including cognitive behavioural therapy (CBT) and person-centred experiential therapy (commonly referred to as counselling for depression; PCE-CfD). Meta-analyses of randomised controlled trials have found psychological treatments for depression at an aggregate level are equally efficacious (Cuijpers et al., 2008; Cuijpers et al., 2013). A large practice-based randomised controlled trial conducted in Talking Therapies sites (the largest provider of psychological therapies in the UK, previously known as Improving Access to Psychological Therapies) found CBT and PCE-CfD to be equally effective at post-therapy (Pybis et al., 2017) a finding replicated in a non-inferiority randomised controlled trial (Barkham et al., 2021) Therefore Talking Therapies routinely offers CBT and PCE-CfD as two of the main front-line treatments for depression (NHS Digital, 2021).

Within Talking Therapies primary mental health care, the main method currently used to guide treatment selection (e.g., deciding between CBT or PCE-CfD for patients with depression) relies on shared decision making. This is a discussion between clinician and patient which positively promotes patient autonomy (Langer et al., 2015; Joosten et al., 2008) but is limited by the lack of personalized evidence-based recommendations. Further, the overall recovery rates for depression across diverse treatments have stagnated at approximately 50% (NHS Digital, 2021; Pybis at el., 2017) despite vast efforts over time to create new psychotherapies or improve current treatments. This implies 1 out of 2 patients accessing any evidence-based treatment usually does not recover from depression, and those accessing treatment are already a minority within those with depression in the general population (McManus et al., 2016).

One line of research that has shown initial promising results to improve psychotherapy outcomes, lies within the area of precision mental healthcare (Delgadillo & Lutz, 2020). Rather than trying to answer the usual question 'which treatment is best?'; precision mental healthcare aims to identify 'which treatment works best for whom under which circumstances?' Better outcomes in depression treatment using only available resources could be gained by *selecting* which treatment is best for each patient at a particular time (Cohen & DeRubeis, 2018).

A prior retrospective study (Delgadillo & Gonzalez Salas Duhne, 2020) identified specific subgroups of patients who had a differential response to CBT and PCE-CfD for depression using artificial intelligence (AI). The results suggest matching people to their optimal treatment model with AI would improve recovery rates. With archival data from 1,435 patients who received either therapy in Talking Therapies services, a targeted prescription algorithm was developed in a training sample using a supervised machine learning approach (elastic net with optimal scaling), and then tested in a statistically independent sample. This study identified the characteristics of a subgroup of patients (approximately 30% of the patients) who if matched to their optimal treatment, CBT or PCE-CfD, were twice as likely to recover (i.e., showed reliable and clinically significant improvement; OR = 2.33) compared to those who received the suboptimal treatment. Another retrospective study developed prediction algorithms to select CBT or PCE-CfD in a sample of 255 Talking Therapies patients. With similarly promising results, patients with a differential treatment response matched to their optimal treatment had better treatment outcome at 6 months and 12 months (Moggia et al., in press).

To date, only one multisite cluster randomised controlled trial has tested the validity of selecting treatment based on a AI data-driven multivariate prediction mode (Delgadillo et al., 2022) found that matching patients to a stratified model of care (i.e., matching more complex patient with higher intensity treatments) improved depression outcomes (OR = 1.40) compared with stepped care (i.e., offering least restrictive and least costly intervention to most patients). The stratified treatment selection model was feasible to implement, with a high adherence rate to the treatment matching rules. Within the stratified care sample, standard cases (i.e., less complex patients) had better outcomes when they were matched to low-intensity treatments. Contrary to expectations, complex cases did not show improved outcomes when matched to high intensity treatments. The authors suggest future research is required to improve outcomes for those at the highest risk of poor treatment response, which often are those who end up being stepped up to high intensity treatments. Therefore, the current study aims to explore within two common high-intensity treatments (CBT and PCE-CfD), which subgroup of patients might be best placed for each treatment to maximize outcomes.

3. Objectives and Hypotheses

3.1. Primary Objective

To pilot the effectiveness of an AI treatment selection model to improve clinical outcomes (i.e., reduce depression) in adults accessing high intensity psychological therapies (CBT or PCE-CfD) for depression in primary mental health services relative to allocation to these two therapies as usual (AAU).

Effectiveness will be defined by comparing reliable and clinically significant improvement (RCSI) in depression between those who received their indicated optimal treatment (treatment selection guided by an AI targeted prescription algorithm alongside shared decision making), and those who received routine clinical care (treatment selection guided only by shared decision making). Only patients with a differential response to treatment will be included. We expect approximately 30% of the sample will be identified as having a differential response based on prior research.

To be clear, the objective is to conduct a preliminary test of the targeted prescription algorithm in helping guide treatment selection, rather than any differential effects between the two high intensity therapies.

3.2. Secondary Objectives

To explore the feasibility and effects of an AI treatment selection model for depression to improve clinical outcomes in adults accessing high intensity psychological therapies (CBT or PCE-CfD) in primary mental health services compared to allocation as usual (AAU).

Throughout the treatment of patients with depression, Talking Therapies services routinely measure common comorbid mental health difficulties, including anxiety and functional impairment. Therefore, these variables were also included in the secondary objectives. Specifically, the secondary objectives will be to assess if TherapyMatch-D differentially impacts on:

- Feasibility:
  - adherence to treatment selection recommendation
  - outcome expectancy
- Effects:

- anxiety symptoms
- functional impairment symptoms
- drop-out rates
- adverse events

3.3. Hypotheses

As a pilot study, no hypothesis testing is undertaken.

4. Methods

4.1. Study Design Overview

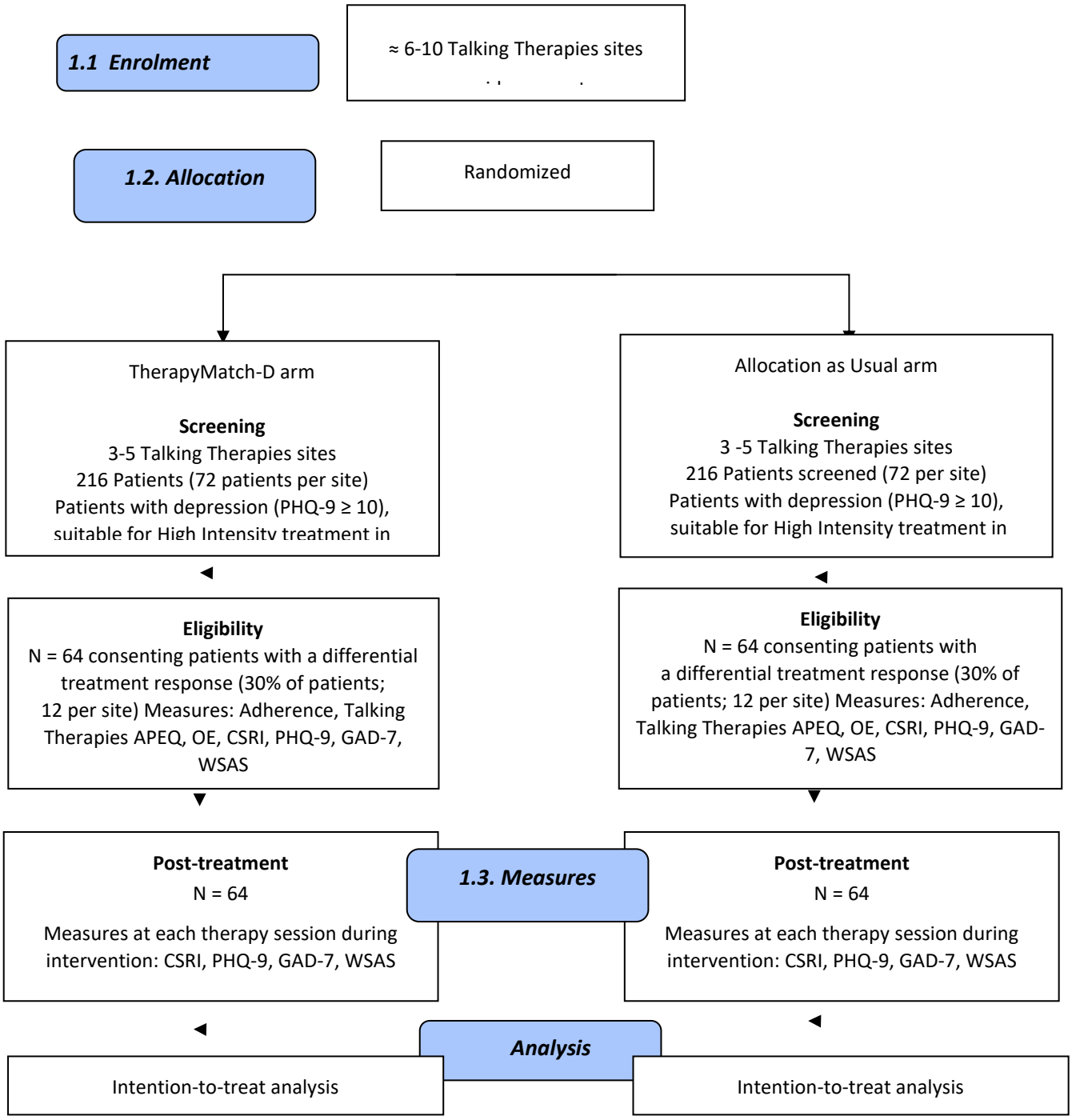
The proposed study is a pilot cluster pragmatic multi-site randomised controlled trial (RCT). Participants will be adults with depression symptoms who seek help at one of the study sites and are suitable for high intensity psychological therapies.

Each participating Talking Therapies site will be stratified according to sociodemographic characteristics and randomly assigned to one of the arms of the RCT: TherapyMatch-D versus AAU. Therapists across both arms will be imputing all consenting patient's data into the TherapyMatch-D computer programme. However, 30% of the cases are expected to show a differential treatment response to treatment according to prior literature (Delgadillo & Gonzalez Salas Duhne, 2020) which are the main group of interest. Differential responders will be identified using the AI targeted prescription algorithm from prior research embedded in the TherapyMatch-D computer programme, and these will the only cases included in the primary data analysis.

In TherapyMatch-D sites, during the initial assessment, differential response cases will be provided with a treatment selection recommendation about their optimal treatment based on the targeted prescription algorithm to be used alongside shared decision making. In AAU sites, during the initial assessment, differential response cases will use only shared decision making to guide treatment selection as occurs routinely in primary care. Non-differential response cases across both arms of the CT will also use only shared decision making to guide treatment selection as per routine care.

Following the initial assessment and treatment selection, subsequent psychological care provision across TherapyMatch-D and AAU (i.e., CFT or PCE-CfD) will be delivered without changes to routine care provision, with the exception of an additional semi structured interview for a subset of patient, as part of a substudy (separate protocol for substudy).

Figure 1. Study flow diagram



4.2 Setting

The study will be conducted across NHS and Non-NHS settings These organisations manage multiple Talking Therapies sites. Talking Therapies is a national programme offering evidence-based psychological interventions for common mental health disorders (mainly depression and anxiety) related conditions (Clark, 2011). Treatment is organised in a stepped care model, which enables access to brief (typically ≤ 8 sessions) and low intensity therapies initially (Step 2), and offers more intensive therapies (up to 20 sessions) for patients who do not improve at the earlier steps of care or are deemed more severe cases at initial assessment (Step 3).

We will only be collecting data from Talking Therapies sites where patients can access both CBT and PCE-CfD at Step 3, which are two of the most common treatments routinely available. We will aim to recruit at least 6 - 10Talking Therapies sites.

4.3 Psychological therapies

Both CBT and PCE-CfD are evidence-based treatments for depression in routine care as recommended by NICE guidelines (2021). The two therapies have different treatment principles and models, but they both follow a standardized national treatment guidelines and competency frameworks (e.g., Roth and Pilling (2008) for CBT; Murphy (2019) for PCE-CfD. Specific procedures for each treatment are detailed elsewhere (National Collaborating Centre for Mental Health, 2020).

They both consist of 12 to 20 sessions for 45 to 60 minutes over four to six months. Patients receiving psychological therapies in Talking Therapies are typically seen in primary care clinics and other community-based venues. Therapies are routinely delivered face-to-face but after the COIVD-19 pandemic, therapies might be delivered over the telephone or online using videoconference. We will monitor and examine potential confounding effects of delivery method for both allocation conditions. Trial participants will therefore be qualified therapists and counsellors that routinely carry out initial assessments in routine Talking Therapies services.

4.4 Randomisation

Randomisation will take place on a site level (cluster). Each participating Talking Therapies site will be stratified and clustered according to demographics and then randomised using electronic randomisation software to either TherapyMatch-D (experimental) or AAU (control) condition. The aim of stratification is to control for sociodemographic characteristics as a potential confounding variable, and to identify a maximally diverse sample.

A site randomisation design has been adopted to minimise the chance of contamination which may occur if randomisation was applied at therapist or patient-level, since it is possible that a clinician who is familiar with the TherapyMatch-D model may apply this knowledge in AAU cases, or share this knowledge with other clinicians from the AAU group. This is particularly relevant in an Talking Therapies service because patients' clinical and demographic data are routinely available to all clinicians. Patients and clinicians will not be blinded to their allocation by virtue of the design.

4.5 Trial arms interventions

1) TherapyMatch-D sites: In differential response cases, therapists during assessment will provide patients with an evidence-based recommendation to guide treatment selection provided by the Digital tool called TherapyMatch-D and use this recommendation alongside shared decision making to select the treatment (CBT or PCE-CfD). Where suitable, the psychological intervention selected will be provided as usual. Non-differential response cases will not be given a treatment recommendation and will follow routine care pathways (i.e., shared decision making) to select suitable treatment.
2) AAU sites: In this condition, all cases (those with and without differential response) will be assigned to treatment following routine care treatment selection (i.e., shared decision making), serving as a control group. Where suitable, the psychological intervention selected will be provided as usual.

Protection from bias

- The trial will be registered prospectively to help ensure full transparency and accountability.
- Independent web-based randomisation software will be used to prevent site selection bias.
- While therapists will likely deduce their site allocation (i.e., if they never receive a treatment recommendation), there is minimal risk of contamination from informal conversations between those taking part in TherapyMatch-D and those in AAU, as all of the therapists within each Talking Therapies site will have the same allocation.
- The trial statistician will remain blinded to site allocation until the data analyses have been completed.

4.6 Eligibility criteria

Talking Therapies Sites
Inclusion criteria
- Talking Therapies site routinely providing CBT and PCE-CfD at step 3.
- Service manager provides informed written consent to enlist the Talking Therapies site and names a lead Local Principal Investigator.

Exclusion criteria
- Lack of any therapists or patients providing informed consent, or lack of consent by service manager.

Therapists/Counsellors
Inclusion criteria
- Be employed by a participating Talking Therapies service on a permanent contract, or be employed as temporary staff with a contract that is at least as long as the expected timescale for the project (1 year)
- Hold a UK recognized qualification and be approved by Talking Therapies to carry out routine assessments in an Talking Therapies service
- Attended a group/individual training on how to utilize the computer programme TherapyMatch-D computer programme.

Exclusion criteria
- Employment contract is shorter than the minimum expected timescale for the study (1 year).
- Currently in training (since they are not yet fully qualified to carry out routine assessments)

Patients
Inclusion criteria
- Adults (18 years of age or older).

- With depression (defined as scoring at least 10 on the PHQ-9), including those with co-morbid anxiety and those taking antidepressant medication (we will monitor and examine potential confounding effects of comorbidity and medication).
- Seeking mental health care in Talking Therapies services at Step 3 (normally via self-referral, GP referral or stepped up from Step 2 low intensity Talking Therapies treatment).
- Deemed eligible for high intensity treatment in Talking Therapies by assessing therapists (patients who do not improve at the earlier steps of care), regardless of any prior mental health treatment from Talking Therapies or elsewhere (we will monitor and examine potential confounding effects of prior treatment and baseline severity).
- Able to take part in the initial assessment in English without the need of interpreters or substantial communication adaptations.

Exclusion criteria

- Patients who are assessed as ineligible for treatment in Talking Therapies (e.g., those who are signposted to other services). Specific criteria for Talking Therapies exclusion is detailed elsewhere (National Collaborating Centre for Mental Health, 2020). Common examples include having other severe mental health disorders, highly acute suicide risk, and comorbid substance use disorder that interferes with the person's ability to engage in therapy.

Note. We will gather information from all consenting participants (216 per arm). However, only those will a differential treatment response as identified by the algorithm in the TherapyMatch-D computer programme, which we estimate would be approximately 30% of the 216 participants (64 participants per arm), will be included in the primary outcome analysis.

4.7 Primary and Secondary Outcomes and Measures

Primary outcome and measure

This study aims to pilot effectiveness of using a targeted prescription to guide treatment selection to improve clinical outcomes in depression relative to AAU, for which the main outcome variable is RCSI in depression. Effectiveness will be measured by the Patient Health Questionnaire-9 (PHQ-9) at the end of the treatment period (last session of CBT or PCE-CfD), with adjustment for baseline depression.

The PHQ-9 (Kroenke et al., 2001) is a brief measure commonly used to monitor the severity of depression and response to treatment. Each of the nine items is scored on a 0–3 scale. Item scores are summed to give an overall severity rating (range 0–27). The PHQ-9 has been validated for use in primary care (Kroenke et al.,2010), with adequate sensitivity (88%) and specificity (88%) estimates for the detection of major depressive disorder using a cut-off score ≥10. RCSI was determined based on the method described by Jacobson and Truax (1991), by combining reliable change index (PHQ ≥6) and diagnostic cut-offs (PHQ-9 <10).

Secondary outcomes and measures

The secondary outcome measures aimed to measure feasibility (adherence to the recommendation provided by the targeted prescription algorithm and outcome expectancy) and effects (anxiety, functional impairment, drop-out rates and adverse events). The specific variables were chosen as additional ways to measure improvement in clinical outcomes, to control for complexity and those variables that were identified to predict a differential response to treatment in the development of the targeted prescription

algorithm, and therefore needed to provide a targeted prescription recommendation of treatment (Delgadillo & Gonzalez Salas Duhne, 2020).

The specific measures for the secondary outcomes are:

- *Adherence to treatment selection recommendation*. In cases with differential response in the experimental arm (TherapyMatch-D), we will monitor and quantify adherence between the treatment selection recommendation and the actual therapy selected by the patient and therapist. This will be measured by a question embedded in the TherapyMatch-D computer programme. After clinicians input clinical and demographic data into the computer programme (at assessment), the computer programme will immediately provide a personalized treatment recommendation where appropriate (if they are part of the TherapyMatch-D intervention group and they are deemed to have a differential response according to past research, which will be determined using the TherapyMatch-D computer programme). Following this recommendation, clinicians will be asked to input on the same computer programme at the end of the session if a treatment has been selected by the patient and therapist, and the specific selected treatment. Clinicians will be asked to write the reasons why they selected a particular treatment, only where the recommended treatment from the computer programme and the selected treatment through shared decision making do not match.
- *Outcome expectancy (OE).* Patients' expectation of therapeutic outcome will be measured by asking "At this point in time, how confident are you that this kind of treatment will work for you on a scale of 0 (not at all) to 10 (definitely)?" There is a reliable relationship between positive expectancy for therapy and better treatment outcomes (Constantino et al., 2018). Scores of 5 or below on this scale are indicative of low expectancy and therefore higher risk of poorer treatment outcomes (Delgadillo et al., 2016).
- *Anxiety*. The Generalized Anxiety Disorder (GAD-7; Spitzer et al., 2006) is a seven-item measure of common anxiety symptoms. 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 generalized anxiety, social phobia, post-traumatic stress and panic disorder (Kroenke et al., 2007). A cut-off score ≥8 in this measure has been shown to detect an anxiety disorder with adequate sensitivity (77%) and specificity (82%).
- *Functional impairment*. The Work and Social Adjustment Scale (WSAS; Mundt et al., 2002) questionnaire assesses the impact of mental health problems on 5 life domains (work, home management, social life, leisure activities, family and relationships) using Likert scales ranging from 0 (no impairment) to 8 (severe impairment). Scores across all 5 domains are summed to derive an overall score of functional impairment.
- *Clinical and demographic variables*. We will gather data relevant for the targeted prescription algorithm: age, employment status, self-reported disability, index of multiple deprivation, ethnicity, chronicity, and antidepressant medication. Additional data collected in routine primary mental healthcare and service utilisation data will include demographics, diagnoses, actual therapy offered, number of therapy sessions, types of treatments offered, reason for discharge, and last step accessed in stepped care system. Basic demographic data will also be collected from therapists (including age, gender, caseload, and qualifications) to explore potential differences in staff providing the intervention.
- *Personality profile*. This information will serve to control for variability in complex cases (Delgadillo et al., 2021) across sites. The Standardized Assessment of Personality–Abbreviated Scale (SAPAS) is an eight-item questionnaire developed to screen for the likely presence of a personality disorder (Moran et al., 2003). Each question prompts respondents to endorse specific personality traits (yes/no), yielding a total score between 0 and 8 where a cut-off >3 is indicative of cases with a high probability of diagnosable personality disorders.

- *Adverse events*. We will record serious and non-serious adverse events such as deaths, self-harm, serious violent incidents, referral to crisis care or admission to psychiatric hospital within both groups. Serious adverse effects related to the trial and unexpected (in accordance with the Health Research Authority guidelines; HRA, 2022), will be reported by Chief Investigator to the appropriate research committee to take appropriate action. The trial relies on standard treatment already provided routinely within primary care services, and all treatments delivered as evidence-based, not experimental. The trial is not changing how the treatment is delivered, and therefore risk management procedures will follow standard Talking Therapies procedures. Although we do not expect adverse effects related to the trial, we will compare rates of reliable deterioration in patients across both arms of the trial to quantify any adverse effects related to the trial.

4.8 Recruitment, study procedures and data collection

Recruitment procedure

Talking Therapies site identification process

- Chief Investigator and researchers will contact NHS Trusts in the Yorkshire and the Humber Virtual Talking Therapies Providers Network via: 1) a short presentation in one of the network meetings and 2) an email with the research proposal inviting them to be involved in the trial.
- Researchers will circulate a research proposal (Appendix) within Talking Therapies sites via email, and request managers interested in collaborating to express an interest. They will also be asked to identify and fill in a contract naming a specific person as a Local Principal Investigator who will act as liaison between our research team and each Talking Therapies site (Appendix).
- The Research Team will organize a meeting with potential Talking Therapies site managers and potential Local Principal Investigators to explain the study, answer any questions, and seek participation and informed consent at Talking Therapies site level. We will send the protocol for sites to make an assessment of capacity and capability, and the sponsor will send a local information pack with the site file, the practicalities of delivering the study and list of roles and responsibilities. A contract agreement will be signed by the sponsor of the study and local R&D/R&I sites.
- After this, Talking Therapies sites will proceed with recruitment of therapists.

Therapist recruitment process

- Local Principal Investigators at each participating Talking Therapies sites will email copies of the participant information sheet (Appendix), consent form (Appendix) and short questionnaire (Appendix) to all therapists conducting initial assessments in their service. This letter will describe the study in general terms and explain what study participation involves as well as the voluntary nature of participation. Local Principal Investigators may also promote the study at their local team meetings (or delegate this task to a colleague). Talking Therapies site collaborators and therapists will also be invited to email or call a member of the research team if they have any further thoughts or questions after team meetings.
- Local Principal Investigators at each Talking Therapies site will invite all their therapists to participate, but any decision to participate in the study will be contracted directly between the therapist and the principal investigator. Therapists will not be pressured by their managers to participate, nor given additional incentives to do so. Therapists will have at least 1 week to consider their participation and to contact the research team to clarify questions, if necessary, prior to the deadline for submitting consent forms.

- Those wishing to participate will be asked to sign electronically the consent form (document will be uploaded on an online platform) sent directly to the research team at the Grounded Research Team. Local Principal Investigators will not receive process consent forms, which will minimise administrative burden but also minimise the potential for selection biases or undue pressure (e.g. therapists feeling that they must consent to participate if their manager is receiving consent forms).
- Consenting therapists will then be invited to participate in a training event (detailed in the study procedure section).

Patient recruitment and consent process

- Participating therapists will log in with a therapist ID in the TherapyMatch-D computer programme, and input the patient pseudonym (non-identifiable ID automatically generated by each of the electronic patient records routinely used in Talking Therapies sites). The TherapyMatch-D computer programme will then guide therapists through a brief and standardised script to provide information and seek verbal consent from patients who they assess in routine care. The script is described in an Appendix. The recruitment script will be read to all patients assessed by participating therapists, during the assessment contact. 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 opt out of the study. Participants will record informed consent in the patient's clinical records.
- If they consent, participants will be asked if the assessing therapist can send them information via email or text about how their data is used by the Talking Therapies service, how to opt-out and how to contact for further questions (the participant information sheet). This link will also include information about the substudy consisting of a semi-structured interview on their view of the treatment selection process (see substudy research protocol, and Appendix on verbal consent process).
- Email will be preferable, but text has been included as an option for inclusion of participants who may not communicate via email. If patients provide their consent, the assessing therapist will send the information sheet for participants via email or text (using a link) within 1 week of their assessment by the assessing therapist.
- If participants refuse to take part in the research, therapists will record the patient's ID in the 'opt-out' section of the TherapyMatch-D computer programme for record purposes. The computer programme will keep a log of how many individuals how many are invited to participate, how many were eligible, and how many refuse.

Study procedure

Organisation of training event

- The research team will liaise with Local Principal Investigators to organise a virtual training session which will be accessed by all therapists regardless of treatment allocation. Training events will be run prior to the start of the study, following a standard training agenda and materials. Researchers will explain the background of the research, the aim and the process on how to use the TherapyMatch-D computer programme, as well as the fundamentals of Good Clinical Practice to gain verbal consent. Consenting therapists will have at least 3 weeks' notice about the training date, to ensure they are able to make necessary arrangements to attend. The training will take approximately 3 hours.
- The research team will produce randomly generated therapist ID numbers to ensure therapist data is fully anonymized and will be given to each therapist prior to the commencement of recruitment of patients.

Intervention: Recommendations for Treatment Selection

At the assessment session, the procedure for treatment selection in the TherapyMatch-D group will be:

- After gaining informed consent, therapists will directly input patient's anonymized data with their unique participant ID to the *TherapyMatch-D* computer programme, and patients pseudonym ID. The electronic care record system used in Talking Therapies sites autonomically assigns each patient a unique pseudonym ID which therapists will be asked to enter this at the beginning of the survey. This list of pseudonyms from *Digital TherapyMatch-D* will be held by the Grounded Research Team (Talking Therapies sites/therapists will not have access to this information), and only each care team will be able to link the pseudonym with the specific patient care record.
- Therapists will have undergone prior training on how to use this tool adequately (see organization of training event). The *Digital TherapyMatch-D* computer programme will be programmed with the targeted prescription algorithm developed in prior research and will provide a treatment recommendation in differential response cases.
- Therapists will be trained to explain their recommendation to patients in a way that shares the current available evidence behind this recommendation, but also enables shared decision-making and which considers patients' preferences. A script will be provided to therapists (Appedix) and shown on the TherapyMatch-D computer programme so therapists may adhere to the script.
- In Talking Therapies sites where there are additional High Intensity Therapies on offer (besides CBT or PCE-CfD), patients will be given a treatment recommendation if there were any, and then follow the same shared decision making to select suitable treatment.
- Due to additional factors guiding treatment selection, not all treatments selected in differential responders will match the optimal treatment recommended. Consequently, the trial will use an intent-to-treat approach. In the Digital TherapyMatch-D, therapists will also be asked to record the actual treatment selected, and the rationale where the recommended treatment and the selected treatment do no match to monitor the factors that led clinicians and patients to choose a different treatment.
- Cases without a differential response identified will not be provided with any treatment selection recommendations, and therefore will follow AAU.

At the assessment session, the procedure for treatment selection in the AAU group will be:

- Therapists will follow the same procedure as above where they input fully anonymized clinical data during the initial assessment into the treatment selection computer programme Digital TherapyMatch-D.
- All cases, including differential response cases, will use the routine treatment allocation process which consist mainly shared decision making between therapist and client, alongside clinical formulation by the assessing therapist, treatment availability, and clinical supervisor's recommendations.

Outcomes, data collection and safeguarding procedures

Talking Therapies services routinely monitor clinical outcomes by asking patients to complete brief standardized symptom questionnaires on a session-to-session basis, which is standard practice (Clark, 2011). These questionnaires are collected by therapists and results are routinely entered into an electronic case record system. All data collection at an item level will be part of routine outcome monitoring except for the semi-structured interviews.

Across both groups (TherapyMatch-D and AAU), patients' data will be collected at the following points in time:

- At assessment, as is routine treatment, patients will be asked to complete the following outcome measures: PHQ-9, GAD-7, WSAS, Outcome expectancy, Personality profile, as well as to provide clinical and demographic variables (detailed in outcome measures).
- Throughout treatment, CBT and CfD therapists will input routinely collected data at each session from the primary and secondary outcome measures to patient record systems used in routine care (e.g., SystemOne and Insight). The research team will also work with a data manager at each of the participating Talking Therapies sites to download a pseudo-anonymized and aggregated dataset from patients, excluding data from patients that did not provide consent. The dataset will include patient-level clinical data nested within therapist caseloads (which will be linked to a unique participant ID).

Throughout treatment, any serious adverse events (SAE) will be reported by the therapist to the Local Clinical Collaborator. Adverse effect is defined as an untoward occurrence that results in death, is life-threating, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, consists of congenital abnormality or birth defects, or is otherwise considered medically significant by the investigator (in line with Safety Reporting for Research other than Clinical Trials of Investigational Medical Products for UK Health Departments' Research Ethics Service (RES) by the Health Research Authority (HRA; 2022). While we do not envision adverse effect related to the current trial for the reasons outline above, as a pilot trial, we will record both serious adverse events (SAE) and non-serious adverse events as defined by the National Research Ethics Service and report them to the appropriate research committee and to take appropriate action. Any serious adverse events (defined by HRA, 2022) should be reported by anyone immediately to the Local Clinical Collaborator who will inform the Chief Investigator upon becoming aware of them, and within 24 hours and following the Good Clinical Pratice (GCP) Guidelines. The local Clinical Collaborator will report within 3 days to the Chief Investigator if it is not urgent, and immediately by telephone if it requires urgent safety measures. The Chief Investigator will discuss within one week with the trial steering committee holding oversight of the study, where researchers alongside the sponsor/committee will seek to determine if a serious adverse event is related to the trial (resulted from administration of any of the research procedures) and unexpected (not listen in the protocol as an expected occurrence). All opinions from the Investigators and Sponsor/Committee will be reported to the Research Ethics Committee within 15 days of the Chief Investigator becoming aware of the event.

Fully encrypted data will be transferred from each Talking Therapies site service to the research team using a secure electronic file transfer. The dataset will be stored in a University of Sheffield secure network drive, which has restricted access to members of the research team. This will ensure the security and adequate storage of research data, consistent with NHS and academic codes of information governance and data protection.

All analyses will be carried out using University of Sheffield computers with up-to-date security software, and data will be held in a restricted-access drive. The study dataset will be held at the University for 10 years after the conclusion of the study.

The end of the data collection will be approximately when the last recruited participant completes their treatment pathway (we envision a total of 2-year active study period). The study will be considered as finalised once the data analysis has been completed as well as the dissemination reports (6 to 12 months after data collection has finished).

5. Data analysis

5.1. Sample size calculation

Pilot trials do not require a formal sample size calculation. However, a sample of at least 64 participants per arm is desirable (Teare et al., 2014) for a binary outcome in a pilot trial. We will aim to recruit 6-10 clusters (3-5 sites randomised in each arm) to allow subsequent sample size calculation for a definitive RCT. Within each Talking Therapies site, we will aim to recruit a minimum of 1 therapist that carry out routine assessment (maximum of 2 therapists per site). Each Talking Therapies site will aim to recruit 64 patients, For this, a total of 432 patients would be screened (216 patients per arm). As we expect approximately 30% of patients across sites to have a differential response, we estimate there would need to be 216 patients screened (64 patients per arm; 216*30% = 64). This calculation is based on the assumption of equal availability for treatment. As a pilot trial, any differences in treatment offer and waiting time for the different treatments will be reported and considered for potential subsequent research.

Overall, we will aim to recruit a minimum of 6-10 therapists that carry out routine assessments across the 6-10 Talking Therapies services (1 to 2 per Talking Therapies service). Between the 6 to 20 therapists, we expect that they will assess at least 432 during a 1-year study period, which would require each therapist to assess 1 to 2 cases per week on average.

5.2. Primary analysis

Patient-level clinical outcome data will be analysed using logistic multilevel modelling conducted according to the intention-to-treat principle according to CONSORT guidelines for Cluster RCTs. Researchers will be blinded to the group allocation while analysing the trial data.

The primary outcome will be defined as reliable and clinically significant improvement (RCSI) in depression symptoms (PHQ-9) after treatment, based on the method described by Jacobson and Truax (1991). A 3-level model will be applied, with patients nested within therapists, nested within Talking Therapies sites, and post-treatment RCSI in depression (PHQ-9) symptoms as the dependent variable. Group (TherapyMatch-D vs. usual care) will be entered as a level-2 predictor, along with baseline PHQ-9 as a level-one covariate. This method will enable us to determine whether TherapyMatch-D is associated with a greater treatment effect (depression symptom reduction) by comparison to usual care and will be specifically run in the target sample of patients identified as having a differential response to treatment. The three-level model will account for the nested structure of the data, as appropriate within a cluster trial design. Given the small sample sizes of this pilot trial, it is unlikely the estimates of random effects for site and therapist will be reliable, but this data may be used to guide subsequent research. If the site and therapist random intercepts are not statistically significant, a one-level parsimonious multivariate regression model will be estimated as a sensitivity analysis. Adjusted odds ratios and confidence intervals will be reported as a primary effect sizes. In addition, we will also report the results in the best fitting model following analyses of goodness of fit to find the most parsimonious model.

We acknowledge that some patients might decide to switch from one therapy to another following allocation in either arm of the trial (i.e., patient allocated to CBT after consenting to treatment asks to switch to PCE-CfD), as occurs in routine practice occasionally. In this pilot trial, we will report the frequency of this occurrence and circumstances. Cases will be included in the primary analysis (as part of the

allocation group to which they were originally allocated to), and secondary analyses will exclude these cases to examine the extent to which this data might contaminate the results. The same reporting and inclusion of cases for primary analyses will be followed in cases where patients and clinicians select another High Intensity Treatment beyond the two examined in this trial.

4.3. **Secondary analyses**

The above modelling strategy will be repeated to compare the rate of improvement (RCSI) in GAD-7 anxiety symptoms, and RCSI in depression symptoms only in the cases who attended at least one treatment session. We will also compare outcome expectancy, dropout rates and adverse effects between groups, and compare characteristics between those who attended at least one treatment session versus those who dropped out following assessment. For both TherapyMatch-D and control groups, we will estimate the proportions of participants who had RCSI post-treatment, and who completed/dropped out of treatment. We will also calculate and report effect sizes for each of the symptom measures (PHQ-9, GAD-7, WSAS) using Cohen's *d* metric (Cohen, 1988), based on mean differences between groups. Treatment attendance, completion, and dropout rates will be presented diagrammatically and based on CONSORT guidelines. To quantify any potential adverse effects related to the trial, we will also calculate a rate of reliable deterioration in patients across both arms of the trial. Further, we will use the data collected to identify complex cases (see StratCare Trial from Delgadillo et al., 2021) and control for variability in complex cases across Talking Therapies sites.

We will examine adherence to the TherapyMatch-D model using the full study sample of participants with a differential treatment response across both arms. Each therapist's Treatment-Matching Precision Score (TMaP) will be calculated, which is a statistical measure of agreement between their observed treatment selection and the recommendations made using the prognostic algorithm. In the experimental group, this would represent the agreement of patients accepting the recommended treatment. In the control group, this is the post-hoc analysis of the agreement the optimal treatment that the prescriptive algorithm would recommend (which patients did not receive, since they were in the control group) and the actual treatment selected via shared decision making. A comparison of mean TMaP scores between groups will be done using parametric or non-parametric tests, depending on the distribution of TMaP scores.

The wider cohort dataset (i.e., non-differential responders who consented to take part in this trial) will be used to examine changes in treatment recommendation patterns over time and treatment outcomes, modelling longitudinal changes in the prevalence of treatment recommendation. These additional analyses with non-differential responders will serve only to maximize the use of available data to inform a future trial, but the results will not be included in the main analyses.

Basic demographic data collected from therapists providing the two psychological treatments to describe the overall workforce (e.g., age, gender, caseload, and qualifications) will be reported in the study, to identify any potential differences in staff providing the intervention. No further analysis of this data is planned a priori. If large differences were found between therapists providing interventions, post-hoc exploratory analysis may be conducted as part of a feasibility trial that may inform future research.

6. Ethical considerations

6.1. Considerations about informed consent

Prior to commencement, ethical approval will be obtained from a National Health Service research ethics committee. The study will also seek Health Research Authority (HRA) approval and R&D permission for NHS staff participants in RDaSH and other participating organisations. The Study will comply with the UK Framework for Health and Social Care Research and ICH-GCP guidelines.

Assessing new patients and making a treatment recommendation are routine procedures in psychological care. However, we expect that the TherapyMatch-D model will support therapists to make treatment recommendations in a more consistent and effective way. We have previously obtained ethical approval for other studies of clinical decision-making tools in which we recruited therapists as primary participants (e.g., Outcome feedback feasibility study REC reference: 15/NW/0675; Talking Therapies Outcome Feedback Trial REC reference: 15/LO/2200). This trial will follow the similar principles, recruitment and training procedures, and –as shown by our previous studies of clinical decision tools– we expect this to be feasible, acceptable and without any major ethical challenges.

In order to obtain informed consent from therapists in line with good clinical practice guidelines, we will take the following steps:

- Meetings with each Talking Therapies site, which will enable potential Talking Therapies managers and assessing therapists with an opportunity to ask questions, raise concerns and discuss any aspects of the study that they wish to clarify.
- Local Principal Investigators at each participating Talking Therapies sites will email copies of the participant information sheet (Appendix), consent form (Appendix) and short questionnaire (Appendix) to all therapists conducting initial assessments in their service. This letter will describe the study in general terms and explain what study participation involves as well as the voluntary nature of participation. Local Principal Investigators may also promote the study at their local team meetings (or delegate this task to a colleague). Talking Therapies site collaborators and therapists will also be invited to email or call a member of the research team if they have any further thoughts or questions after team meetings.
- Local Principal Investigators at each Talking Therapies site will invite all their therapists to participate, but any decision to participate in the study will be contracted directly between the therapist and the principal investigator. Therapists will not be pressured by their managers to participate, nor given additional incentives to do so. Therapists will have at least 1 week to consider their participation and to contact the research team to clarify questions, if necessary, prior to the deadline for submitting consent forms.
- Those wishing to participate will be asked to sign electronically the consent form (document will be uploaded on an online platform) sent directly to the research team at the Grounded Research Team. Local Principal Investigators will not receive process consent forms, which will minimise administrative burden but also minimise the potential for selection biases or undue pressure (e.g. therapists feeling that they must consent to participate if their manager is receiving consent forms).
- Consenting therapists will then be invited to participate in a training event (detailed in the study procedure section), where they will be provided with further information, have an opportunity to raise questions and further clarify any aspect of the research. They will also be explained how to seek informed consent from patients, and guidelines on how to provide a treatment recommendation and use shared decision making to reach a final decision on treatment alongside the client.
- Neither Talking Therapies sites, therapists nor participants will receive any financial incentive to participate.

In order to obtain informed consent from patients in line with good clinical practice guidelines, we will take the following steps:

- Participating therapists will use a brief and standardised script to provide information and seek verbal consent from patients who they assess in routine care. The script is described in the Appendix 'Consent Process Patients'. 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 therapists, during the assessment contact. 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 opt out of the study.
- If they consent, participants will be asked if the assessing therapist can send them information via email or text about how their data is used by the Talking Therapies service, how to opt-out, how to contact for further questions (the participant information sheet), and information about the substudy. Email will be preferable, but text has been included as an option for inclusion of participants who may not communicate via email. If patients provide their consent, the therapist will record their anonymised assessment information in a secure and confidential patient record system which is used in routine care, and the assessing therapist will send the information sheet for participants via email or text (using a link). Therapists will also input into the TherapyMatch-D computer programme the anonymized patient information needed for the study (which does not include emails/telephone number). Emails and telephone numbers will only be collected by the Talking Therapies services as part of routine care, and researchers will not have access to this information.
- The link to the online participant information sheet will be sent within 1 week of their assessment by the assessing therapist. The participant information sheet explains how participants' anonymised information will be used for research purposes, and how they can withdraw from the study or make complaints. In the patient information sheet, patients will be advised of their right to withdraw from the study and the right to request their data to be deleted from the study dataset up until 1 week after the last data has been collected from them (1 week after after the last session of psychological therapy). After this point it will not be possible for participants to withdraw their individual data. This will be explicit in the electronic participant information sheet and in the consent form.
- If participants refuse to take part in the research, therapists will record the patient's ID in the 'opt-out' online TherapyMatch-D tool for record purposes. Participants will not be asked the reasons why they decided not to participate. Therapists will keep a log of how many individuals how many are invited to participate, how many were eligible, and how many refuse.
- Participating therapists will also send information via text/email (in the same link as the main study information sheet) about the substudy consisting of a semi-structured interview regarding their view on the treatment selection process (see substudy research protocol, and Appendix on verbal consent process).
- In the experimental group, for about 30% of the patients the computer programme will provide a treatment recommendation which the therapist will discuss with their patient (see treatment selection process script), and then use usual shared decision making to reach a final decision on treatment. Patients do not have to follow the recommendation provided if either the therapist or the patient do not think it is suitable.
- Potential patients will be advised of their right to refuse or withdraw verbally, without there being any impact to their subsequent treatment.
- Neither Talking Therapies sites, therapists nor participants will receive any financial incentive to participate.

6.2. Considerations about confidentiality and anonymity of clinical records

We will gather fully de-identified clinical data for patients accessing this clinical service, and which is already gathered in routine practice by Talking Therapies services. These data will include demographics (e.g. age, gender, ethnicity, employment status, index of multiple deprivation) and clinical care data (e.g. diagnoses, number of therapy sessions, types of treatments offered, reason for discharge, last step accessed in stepped care system).

Electronic consent forms from therapists and their ID number will be stored in secure password protected University of Sheffield secure network drive (with restricted access to members of the research team), along with records of anonymized patient ID spreadsheets (specifying those who gave their verbal consent and those who refused to take part). Patient data with a non-identifiable pseudonym for each patient containing fully de-identified therapist and clinical caseload records will also be kept in the secure University network drive. The participating therapists' pseudonym ID will be linked to the clinical patient record system via the TherapyMatch-D computer programme. Pseudo-anonymised study data (for therapists and their patients) will be stored in secure University network drives for data analysis purposes. Electronic data will be retained and securely stored until the end of the trial, and then archived by the sponsor. Serious adverse event forms if necessary, will be also securely stored in University Network drive. The final and fully anonymised study dataset will be stored in a secure University network drive which is password protected and only restricted to specific users in the research team for up to 10 years after conclusion of the study.

We consider that our proposed method (described in study protocol) for aggregating and analysing fully anonymized patient data is congruent with the NHS information governance policy General Data Protection Regulation, and good clinical practice guidelines. We will also obtain verbal consent from patients and they will have immediate online access to information on how to withdraw their data from the study if they wish to do so.

6.3. Considerations about treatment provided and adverse event management

Patients will receive one of two NICE recommended psychological therapies for depression, which are already provided as routine standard care within each site and are not experimental. Diverse studies have shown that CBT and PCE-CfD are safe, effective, tolerable and acceptable to patients (Pybis et al., 2017)[35]. No treatment will be withheld to participants in this trial, nor will changes to treatment be made due to this trial. During initial assessment and at each treatment session, the therapist will review the questionnaires (most of which are part of the routine care) and act in accordance with clinical and Trust guidance to safeguard clients and manage risk appropriately. Risk management procedures (e.g., suicidality and safeguarding issues) will follow standard Talking Therapies procedures.

Patients in the experimental arm and with a differential response will be provided with a treatment selection recommendation, but they will still be making the final decision with their assessing therapist about their treatment. Should patients decide they wish to switch treatment modality after a shared decision was made, as occurs in routine practice occasionally, usual local procedures will be followed (data management of these participants is provided on section 5.2). Patient choice and empowerment are core values of this trial, alongside providing the treatment with the higher chance of success according to the best available evidence.

Further, we will record both serious and non-serious adverse events as defined by the National Research Ethics Service (e.g., deaths, self-harm, serious violent incidents, referral to crisis care or admission to psychiatric hospital) within both groups, report them to the appropriate research committee and to take appropriate action. Any serious adverse events (defined by HRA, 2022) will be reported by the therapist to the Local Clinical Collaborator. The Local Clinical Collaborator will report within 3 days to the Chief Investigator if it is not urgent, and immediately by telephone if it requires urgent safety measures. The Chief Investigator will discuss within one week with the trial steering group, where independent researchers will aid the decision making if a SAE is related to the trial (resulted from administration of any of the research procedures) and unexpected (not listen in the protocol as an expected occurrence). If the SAE is deemed to be related and unexpected, the Chief investigator will report to the Research Ethics Committee within 15 days of the Chief Investigator becoming aware of the event.

The trial relies on standard treatment already provided routinely within primary care services, and all treatments delivered as evidence-based, not experimental. The trial is not changing how the treatment is delivered, and therefore risk management procedures will follow standard Talking Therapies procedures. Although we do not expect adverse effects related to the trial, we will compare rates of reliable deteriorate in patients across both arms of the trial to quantify any adverse effects related to the trial.

There will be a trial steering committee to ensure governance in accordance with Data Monitoring and Ethics Committee (DMEC) guidelines. Researchers will invite independent researchers with expertise in the field of RCTs in mental health. They will meet regularly to ensure ethical and safe procedures, and any adverse events will be discussed in this Committee.

6.4. Technology and information governance

This trial will be using a computer programme called TherapyMatch-D. This computer programme has been designed by expert computer programmers to support this study, and can be accessed securely in any device with internet, which is usually be the clinician's laptop or work mobile. The computer programme will enable therapists to input some basic information that is routinely gathered at initial mental health assessments (e.g., age, ethnicity, severity of depression and anxiety, severity of functional impairment, personality traits, diagnosis). The computer programme enters these data into an algorithm which classifies cases in three groups: recommended CBT, recommended PCE-CfD, or no recommendation. The algorithm was developed in a previous research study (see reference below), which recommended about 30% of patients might be best placed for one therapy over another. The TherapyMatch-D computer programme is fully compliant with NHS information governance and data protection regulations, in the following way:

- The computer programme does not require any personally identifiable information from therapists or patients.
- The programme will not be publicly available online during the trial, it has password-restricted access for registered users (participating therapists, and researchers).
- The programme will store a record every time that it is used, in order to enable the researchers to monitor progress with the trial. The data does not contain any personally identifiable information; it only stores the date/time, inputs (e.g. anonymized patient diagnosis and demographics), and outputs (e.g. a treatment recommendation provided to the user). These records will be stored in a password protected and secure network drive at the University of Sheffield.
- Each record will be linked to a randomly generated user code (provided to each participating therapist). This will enable us to link the computer programme data with clinical records at the end of the study.

- In summary, the computer programme will simply help therapists to generate treatment recommendations using an evidence-based algorithm, and it will help the research team to track utilisation and progress with the trial. All data is pseudo-anonymized.

Finally, this trial has not been considered as testing a medical device because the main aim is to explore feasibility and acceptability of an experimental device. The treatment selection algorithm is currently at an experimental stage rather than a definitive Randomised Controlled Trial to be used for treatment which if successful, would be the subsequent stage.

7. References

Barkham, M., Saxon, D., Hardy, G. E., Bradburn, M., Galloway, D., Wickramasekera, N., ... & Brazier, J. E. (2021). Person-centred experiential therapy versus cognitive behavioural therapy delivered in the English Improving Access to Psychological Therapies service for the treatment of moderate or severe depression (PRaCTICED): A pragmatic, randomised, non-inferiority trial. *The Lancet Psychiatry, 8(*6), 487-499.

Clark, D. M. (2011). Implementing NICE guidelines for the psychological treatment of depression and anxiety disorders: The IAPT experience. *International Review of Psychiatry, 23*, 318–327. doi:10.3109/09540261.2011.606803

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillside, NJ: Lawrence Erlbaum Associates.

Cohen, Z. D., & DeRubeis, R. J. (2018). Treatment selection in depression. *Annual Review of Clinical Psychology*, *14,* 209-236. doi:10.1146/annurev-clinpsy-050817-084746

Constantino, M. J., Vîslă, A., Coyne, A. E., & Boswell, J. F. (2018). A meta-analysis of the association between patients' early treatment outcome expectation and their posttreatment outcomes. *Psychotherapy*, *55*(4), 473.

Cuijpers, P., Berking, M., Andersson, G., Quigley, L., Kleiboer, A., & Dobson, K. S. (2013). A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. *The Canadian Journal of Psychiatry, 58*(7), 376-385. https://doi.org/10.1177/070674371305800702

Cuijpers, P., Van Straten, A., Andersson, G., & Van Oppen, P. (2008). Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. *Journal of Consulting and Clinical Psychology, 76*(6), 909. http://dx.doi.org/10.1037/a0013075

Delgadillo, J., & Gonzalez Salas Duhne, P. (2020). Targeted prescription of cognitive–behavioral therapy versus person-centered counseling for depression using a machine learning approach. *Journal of Consulting and Clinical Psychology*, *88*(1), 14-24. doi:10.1037/ccp0000476

Delgadillo, J., & Lutz, W. (2020). A Development Pathway Towards Precision Mental Health Care. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2020.1048

Delgadillo, J., Ali, S., Fleck, K., Agnew, C., Southgate, A., Parkhouse, L., ... & Barkham, M. (2022). Stratified care vs stepped care for depression: A cluster randomized clinical trial. *JAMA Psychiatry*, 79(2), 101-108. doi:10.1001/jamapsychiatry.2021.3539

Delgadillo, J., Moreea, O., & Lutz, W. (2016). Different people respond differently to therapy: A demonstration using patient profiling and risk stratification. *Behaviour Research and Therapy*, *79*, 15-

Jacobson, N. S. and Truax, P. (1991). Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology*, 59, 12–

Joosten, E. A. G., Defuentes-Merillas, L., De Weert, G.H., Sensky, T., Van Der Staak, C.P.F., & De Jong, C.A.J. (2008). Systematic review of the effects of shared decision-making on patient satisfaction, treatment adherence and health status. *Psychotherapy and Psychosomatics, 77*(4), 219-26.

Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2001). The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine*, 16, 606–613.

Kroenke, K., Spitzer, R. L., Williams, J. B. W., & Löwe, B. (2010). The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: A systematic review. *General Hospital Psychiatry*, 32, 345–359.

Kroenke, K., Spitzer, R. L., Williams, J. B. W., Monahan, P. O., & Löwe, B. (2007). Anxiety disorders in primary care: Prevalence, impairment, comorbidity, and detection. *Annals of Internal Medicine*, 146, 317–325.

Langer, D. A., Mooney, T. K., & Wills, C. E. (2015). Shared decision-making for treatment planning in mental health care: Theory, evidence, and tools. *Web: Oxford Handbooks Online*.

McManus, S., Bebbington, P. E., Jenkins, R., & Brugha, T. (2016). *Mental Health and Wellbeing in England: the Adult Psychiatric Morbidity Survey 2014*. NHS digital.

Moggia, D., Saxon, D., Lutz, W., Hardy, G. E., Barkham, M. Person-Centered Experiential Therapy or Cognitive-Behavioral Therapy? Which One for Whom for the Treatment of Depression in the English Improving Access to Psychological Therapies Service. In press.

Moran, P., Leese, M., Lee, T., Walters, P., Thornicroft, G., & Mann, A. (2003). Standardised Assessment of Personality–Abbreviated Scale (SAPAS): Preliminary validation of a brief screen for personality disorder. *British Journal of Psychiatry, 183*, 228–232.

Mundt, J. C., Mark, I. M., Shear, M. K., Griest, J. M. (2002). The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *British Journal of Psychiatry*, *180*, 461-464.

Murphy, D. (2019*). Person-centred experiential counselling for depression: A manual for training and practice.* London, UK: SAGE Publishing.

National Collaborating Centre for Mental Health. (2020 May). *The Improving Access to Psychological Therapies Manual.* NHS England. https://www.england.nhs.uk/wp-content/uploads/2020/05/iapt-manual-v4.pdf

National Institute for Health and Care Excellence (NICE), 2021. *Depression in Adults: Recognition and Management: Clinical Guideline* [CG90]. Retrieved from: https://www.nice.org.uk/guidance/cg90

NHS Digital. (2021). Psychological Therapies: Additional analyses of therapy-based outcomes in IAPT services (England 2020-21 experimental statistics). London, UK: Health and Social Care Information Centre.

Pybis, J., Saxon, D., Hill, A., & Barkham, M. (2017). The comparative effectiveness and efficiency of cognitive behaviour therapy and generic counselling in the treatment of depression: evidence from the 2nd UK National Audit of psychological therapies. *BMC Psychiatry, 17*(1), 215. doi:10.1186/s12888-017-1370-7

Roth, A. D., & Pilling, S. (2008). Using an evidence-based methodology to identify the competences required to deliver effective cognitive and behavioural therapy for depression and anxiety disorders. *Behavioural and Cognitive Psychotherapy*, *36*(2), 129-147. doi:10.1017/S1352465808004141

Spitzer, R., Kroenke, K., Williams, J. B. W., & Lowe, B. (2006). A brief measure for assessing generalized anxiety disorder: The GAD-7. *Archives of Internal Medicine*, 66, 1092–1097.

Teare, M. D., Dimairo, M., Shephard, N., Hayman, A., Whitehead, A., & Walters, S. J. (2014). Sample size requirements to estimate key design parameters from external pilot randomised controlled trials: a simulation study. Trials, 15(1), 1-13.

World Health Organization. (2017). *Depression and other common mental health disorders: global health estimates.* Geneva: World Health Organization.