BMC Psychiatry

STUDY PROTOCOL

Open Access

Optimizing treatment for depression in primary care using psychotherapy versus antidepressant medication in a low-resource setting: protocol for the OptimizeD randomized controlled trial

Julia R. Pozuelo[1,2,3*], Anuja Lahiri[4], Rahul S. P. Singh[4], Arvind Kushwah[4], Mimansa Khanduri[4], Akanksha Shukla[4], Azaz Khan[4], Sruthi G.[4], Varun Shende[4], Yashika Parashar[1], Yashwant K. Mehra[4], Anant Bhan[4], Ronald C. Kessler[5], Daisy R. Singla[6,7,8], John A. Naslund[1], Karmel W. Choi[9,10], Pim Cuijpers[11,12], Robert DeRubeis[13], Mohammad M. Herzallah[14,15], Chunling Lu[1,16], Jordan W. Smoller[9,10,17], Tyler J. VanderWeele[18], Abhijit R. Rozatkar[19], Tamonud Modak[19], Michelle Melwyn Joel[19], Debasis Biswas[19], Shubham Atal[19], Umay Kulsum[19], Steven D. Hollon[20†] and Vikram Patel[1,18†]

Abstract

Background Psychotherapy and antidepressant medications are first-line treatments for depression, and they both have significant treatment effects on average. However, treatment response varies widely across patients, and neither approach is universally effective. Identifying the most effective treatment for each patient is critical everywhere, but particularly in low-resource settings where access to mental health care is limited. The Optimizing Depression (OptimizeD) trial aims to explore whether different patients respond differently to behavioral activation therapy versus antidepressant medication and if providing each patient with their optimal treatment improves outcomes in primary care.

Methods We plan to randomize 1,500 patients with moderate to severe depression (defined as a Patient Health Questionnaire [PHQ-9] score ≥ 10) from primary healthcare settings in Bhopal, India, with equal allocation either to a culturally adapted behavioral activation therapy delivered by trained counselors (Healthy Activity Program) or to antidepressant medication (fluoxetine). Treatment will last 3 months, with remission (defined as PHQ-9 score < 5) at 3 months as the primary endpoint. Using machine learning, we will attempt to develop a precision treatment rule that leverages baseline clinical, psychological, cognitive, socioeconomic, and biological data to predict which treatment is most likely to achieve remission for each patient. Cost-effectiveness analysis will then assess whether the added costs of optimizing treatment are justified by improvements in remission, recovery, and cost savings at the health system and societal levels. Secondary and exploratory objectives include assessing the effectiveness

†Steven D. Hollon and Vikram Patel denotes joint senior author.

*Correspondence:
Julia R. Pozuelo
julia_ruizpozuelo@hms.harvard.edu
Full list of author information is available at the end of the article

of optimization in a range of secondary outcomes, evaluating treatment mechanisms, and exploring whether incorporating genetic and biological markers as predictors improves treatment optimization.

Discussion The OptimizeD trial will evaluate whether baseline information collected in routine care can inform optimal depression treatment selection and identify predictors of nonresponse to facilitate timely specialist referrals. Findings have the potential to enhance personalized depression care in primary health systems, particularly in low-resource settings, with broader implications for global public health.

Trial registration ClinicalTrials.gov (NCT05944926; registered July 2, 2023) and Clinical Trials Registry India (CTRI/2024/01/061932; registered January 29, 2024).

Keywords Depression, Primary care, Behavioral activation, Antidepressants, Precision mental health, India

Background

Depression is a common mental disorder and a leading cause of disability [1, 2]. The burden is particularly pronounced in low-resource settings, where access to mental health services remains limited [3, 4]. Primary care facilities often serve as the first—and frequently only—point of contact for individuals with depression, yet the condition remains vastly underdetected and undertreated [5]. This treatment gap contributes to adverse social, economic, and health outcomes, with far-reaching implications for individuals, families, and society as a whole [6–10].

Depression is treatable, and the World Health Organization recommends two first-line treatments for moderate to severe depression in primary care: (1) brief psychological therapy (such as behavioral activation) and (2) generic antidepressant medications (such as fluoxetine) [11, 12]. Meta-analyses support these recommendations, showing that both have significant treatment effects on average [13, 14].

Despite the availability of effective interventions, two fundamental challenges complicate efficient resource allocation [15]. First, individual responses vary significantly, with fewer than 25% of patients achieving remission with initial treatment [16–20]. This heterogeneity in response makes it difficult to determine the most suitable option for each patient without relying on trial and error. Second, more than half of patients may not respond to either treatment, yet identifying these refractory cases early to facilitate timely referral to specialist care remains complex [21, 22]. Consequently, many patients whose initial treatment fails never proceed to more effective interventions, increasing the risk of chronicity and prolonged impairment [23]. These challenges are particularly acute in low-resource settings, in which ineffective first-line treatment carries high opportunity costs and diverts scarce mental health resources from more effective uses [3, 4, 24].

Precision mental health has emerged as a promising approach to addressing these challenges by identifying patient characteristics associated with differential treatment response and developing algorithms to guide personalized treatment selection and referral pathways [25–27]. Early research in this domain focused on individual predictors of treatment response, such as depression subtype or severity, but no single indicator has proven adequate to inform clinical decisions meaningfully [17, 28, 29]. Recent advances in statistical methodology and machine learning now allow researchers to process numerous patient variables simultaneously, developing personalized prediction algorithms that improve allocation accuracy [17, 25, 30–35]. Such approaches can be especially valuable in settings with limited resources, in which precision treatment rules may inform not only which treatment to offer but also who should be prioritized for treatment when resources are limited.

Despite these promising developments, several gaps remain. First, most studies have small sample sizes, limiting power to detect moderation and reducing prediction accuracy [25, 36]. Second, many studies assess only a limited set of characteristics, making it difficult to identify which factors predict differential treatment response, highlighting the need for broader baseline assessments that can later be refined [17]. Third, most precision treatment research has been conducted in specialized mental health facilities in high-income settings, limiting its relevance to low-resource primary care [37, 38]. Fourth, many existing precision approaches rely on advanced diagnostic technologies (e.g., genetic markers, neuroimaging) that are impractical for widespread implementation in low-resource primary care settings [39, 40].

Study objectives

The Optimizing Depression (OptimizeD) trial aims to address these gaps by developing and validating a precision treatment approach for depression in primary care settings in India. The study will randomize 1,500 patients with moderate to severe depression to receive either a culturally-adapted behavioral activation

psychotherapy (Healthy Activity Program, HAP) [41, 42] or antidepressant medication (ADM, fluoxetine). We will then use machine learning methods to investigate whether a useful precision treatment rule (PTR) can be developed to predict differential treatment response based on baseline patient characteristics.

The OptimizeD trial explores several novel innovations. Unlike many precision mental health studies that rely on complex biomarkers or expensive neuroimaging techniques, we focus on self-reported measures that are simple, scalable, and feasible to implement in routine primary care. These include variables spanning multiple domains—clinical, psychological, cognitive, and socioeconomic—reflecting depression's multifaceted nature [43]. Each baseline variable being considered meets three essential criteria: (1) prior evidence or theory suggesting that the variable might predict differential treatment outcome; (2) cross-cultural applicability; and (3) feasibility of collection in primary care settings. With a sample of 1,500 participants, the study is well-powered to detect meaningful treatment moderators and validate findings in an independent subsample [36]. Beyond developing the PTR, we will identify baseline predictors of treatment nonresponse to guide specialist referrals and evaluate the cost-effectiveness of optimal versus non-optimal treatment assignment. The inclusion of long-term follow-up will determine whether treatment assignment to optimize 3-month outcomes also improves sustained recovery. Additionally, two exploratory aims will extend the study's impact: investigating potential treatment mechanisms through mediation analysis and examining whether biological markers can enhance prediction accuracy when added to the PTR.

Overall, the OptimizeD trial will serve as a proof-of-concept for applying precision mental health principles in primary care settings in low-resource environments. Success in developing a scalable, data-driven approach to treatment selection would have the potential to shift practice in mental health care away from a "one-size-fits-all" trial-and-error approach to a more personalized, evidence-based approach that optimizes outcomes while maximizing efficiency.

The overarching goal of this study is to improve depression outcomes in primary care by determining the preferred treatment between two practical alternatives for each patient. The primary objectives focus on assessing the effectiveness of optimizing treatment in achieving remission and evaluating cost-effectiveness at 3 months. Secondary objectives evaluate the effectiveness of optimization in improving secondary outcomes. Exploratory objectives include examining potential mediators and assessing biological predictors to enhance treatment prediction (Table 1).

Methods

Trial design

The OptimizeD trial is a phase III, single-blind, two-arm, parallel-group randomized precision trial. Eligible participants will be randomized to either treatment modality (HAP vs. ADM) in a 1:1 ratio. The protocol conforms to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT 2025) guidelines [44] (see checklist in Table A1 in the supplementary information).

Study setting

The study is currently being implemented in Bhopal district, located in Madhya Pradesh, a state in central India with a population of over 87 million, of whom nearly 73% reside in rural areas [45, 46]. This state ranks among the lowest on the Human Development Index and last on the Global Hunger Index among all Indian states [47, 48].

The recruitment sites comprise 8–14 public sector Primary Healthcare Facilities in Bhopal, selected based on a set of predefined criteria: availability of a Medical Officer authorized to prescribe antidepressants, presence of a pharmacist, proximity to the laboratory for biological specimen storage, and availability of a private room for assessments. Centers meeting the highest number of criteria were prioritized for inclusion. Prior research in similar facilities identified a 17% point prevalence of moderate to severe depression [49, 50].

Eligibility criteria

Inclusion criteria for this trial are: (1) Provision of signed and dated informed consent form; (2) Age 18 or above; (3) Attend one of the selected Primary Health Care Facilities in the study setting; and (4) A score of 10 or above on the Patient Health Questionnaire-9 (PHQ-9) [51]. Exclusion criteria of this trial are: (1) Women who are pregnant or are breastfeeding or lactating; (2) Patients with a history of psychosis, including schizophrenia spectrum disorders or bipolar disorder; (3) Patients planning to permanently move out of the study area during the follow-up period; (4) Patients with evidence of cognitive impairment based on the Mini-Mental State Examination-2 (MMSE-2 Brief Version) [52]; (5) Patients who do not speak either English or Hindi (the latter being the primary language of the region); (6) Patients undergoing treatment for depression at the time of recruitment or who completed treatment within one month prior to recruitment; (7) Patients at imminent risk for suicide as determined by the Columbia Suicide Severity Rating Scale (C-SSRS) and the assessment of the trial psychologist and/or trial psychiatrist

Table 1 OptimizeD trial objectives, endpoints, and hypotheses

Objectives	Endpoints	Hypothesis
Primary		
1. Clinical Outcomes: To evaluate the effectiveness of optimization via generating a PTR on patients with moderate to severe depression randomized to either HAP or ADM. We will use machine learning to develop the PTR, using a wide range of characteristics measured at baseline as predictors	The primary endpoint will be remission from depression symptoms, defined as a PHQ-9 score of less than five at the 3-month follow-up	We hypothesize that patients allocated to their optimized treatment will be significantly more likely to remit (3-month outcome) than patients who are either allocated randomly or allocated to the treatment that has the higher average treatment effect
2. Cost-effectiveness Outcomes: To conduct a cost-effectiveness analysis by comparing relative costs and effectiveness between those who were randomly allocated to their optimal treatment with those who were randomly allocated to a non-optimal treatment, based on the PTR developed in Objective 1	Cost-effectiveness analysis at the 3-month follow-up. To compute this, we will assess the costs of optimal vs. non-optimal treatments. Effectiveness will be measured by (1) likelihood of remission (PHQ-9 < 5) and (2) Quality-adjusted life years (QALYs) using WHODAS-II. Costs will be measured using the Client Service Receipt Inventory (CSRI) and system-level costs	We hypothesize that optimizing will be cost-effective compared with random assignment
Secondary		
To evaluate the effectiveness of optimization in improving secondary outcomes	Improvement in secondary outcomes including severity (PHQ-9), anxiety (GAD7), disability (WHODAS-II), patient-rated change, and well-being (WHO5) at the 3-month follow-up	We hypothesize that patients allocated to their optimized treatment will show greater improvement in secondary outcomes compared to those allocated to non-optimal treatment
To evaluate the effectiveness of optimization in the long-term	Recovery from depression symptoms is defined as going nine months without relapse (PHQ-9 ≥ 5) following remission. The endpoint will be at the 12-month follow-up	We hypothesize that patients allocated to their optimized treatment will be more likely to recover (12-month outcome) than patients who are allocated to their non-optimal treatment
Exploratory		
Mediators: To explore potential mediators across different patient groups and treatments	Anhedonia (SHAPS), Patient's activation (PAAS), Rumination (ARQ), Anxiety (GAD7), Loneliness (UCLA), Sleep (BPSQI), at baseline, weeks 1.5, 6, 12, month 12	We hypothesize that the inclusion of our PTR in interaction terms with our purported mediators should facilitate the detection of moderated mediation among patients who show specificity of response. This exploratory aim will offer insights about mechanisms of action for each treatment
Biological Predictors: To explore whether polygenic risk scores and other biomarkers can enhance our prediction of both general and differential response to either treatment	Polygenic risk scores for depression; inflammatory marker (CRP); one candidate gene related to pharmacogenetics (CYP2D6) at baseline	We hypothesize that incorporating polygenic risk scores and other biomarkers into the PTR will enhance its predictive utility

ADM Antidepressant Medication, *ARQ* Analytical Rumination Questionnaire, *BPSQI* Brief Pittsburgh Sleep Quality Index, *CSRI* Client Service Receipt Inventory, *CRP* C-reactive Protein, *GAD-7* Generalized Anxiety Disorder-7, *HAP* Healthy Activity Program, *PAAS* PREMIUM Abbreviated Activation Scale, *PHQ-9* Patient Health Questionnaire-9, *PTR* Precision Treatment Rule, *QALYs* Quality-Adjusted Life Years, *SHAPS* Snaith-Hamilton Pleasure Scale, *UCLA* UCLA Loneliness Scale, *WHODAS-II* World Health Organization Disability Assessment Schedule-II, *WHO-5* World Health Organization Well-Being Index

[53]; and (8) Patients from households in which another member has been recruited into the study. There are no exclusions for other nonpsychotic comorbidities or other medical conditions, and no exclusions based on race, ethnicity, caste, or religion.

Study procedures

Recruitment is conducted by trained and supervised Research Assistants (RAs) who approach individuals attending primary healthcare facilities. Potential participants are introduced to the study and invited to complete an eligibility survey administered electronically via tablet using Research Electronic Data Capture (REDCap) [54]. The survey follows a stepwise format, beginning with the PHQ-2 and expanding to the full PHQ-9 for those scoring ≥ 1. Individuals who endorse the 9th item of the PHQ-9 (score ≥ 2) complete the C-SSRS [53], and those identified as high-risk are referred to the trial psychologist and/or trial psychiatrist. Patients determined to be at imminent risk for suicide (e.g., those requiring hospitalization) are excluded from the study. If not deemed at imminent risk and otherwise eligible, the participant may proceed with recruitment. Additional questions assess

exclusion criteria such as psychiatric history and plans to relocate, among others.

Those who meet all eligibility criteria and provide consent are invited to complete the baseline assessment, which includes questionnaires, neurocognitive tasks, and biospecimen collection. The assessment covers multiple domains, including clinical (e.g., depression severity, comorbidities), psychological (e.g., personality traits), cognitive (e.g., attention, memory), socioeconomic (e.g., education, income), and biological (e.g., genetic and inflammatory markers). The full assessment schedule is detailed in Table 2. The OptimizeD baseline battery was developed through a systematic, multimethod process aimed at balancing breadth and brevity. The process involved updating a systematic review to identify constructs associated with differential treatment response, conducting an expert survey to refine the list, and selecting culturally appropriate and scalable measurement tools. The initial battery was piloted with 200 participants, and data from the pilot were used to reduce redundancy and streamline the assessment through exploratory factor analysis and machine learning techniques. This optimization reduced administration time by 27% while retaining key constructs. Table A2 presents the final set of measures included in the baseline battery. A detailed description of the development process will be provided in a separate publication.

To explore whether genetic and biomarker data can improve treatment response prediction, participants are also invited to provide a 5 mL intravenous blood sample for genetic/biomarker analysis. Participation in the blood draw is optional and not required for inclusion in the trial. For those unwilling or unable to provide a blood sample, a 1 mL saliva sample is requested as a non-invasive alternative.

Immediately following this assessment, participants are randomized to one of the two treatment arms. Study assessments occur at weeks 1.5, 6, and 12, with follow-up assessments at 6, 9, and 12 months. Primary and secondary outcomes – remission, cost-effectiveness, severity, anxiety, disability, patient-rated change, and well-being – are assessed at 3 months. Recovery is assessed at the 12-month follow-up. Measurement tools are detailed in Tables 1 and A2. All study assessments, except for the eligibility survey and baseline assessment, are conducted by outcome assessors. Suicidal behavior is assessed at all time points, and those identified as high risk are referred to the trial psychologist/psychiatrist for further evaluation. The trial design is presented in Fig. 1.

Randomization and blinding

Participants are randomized in a 1:1 ratio to either HAP or ADM using a computerized algorithm developed by the Centre for Healthcare Randomised Trials (CHaRT) at the University of Aberdeen [55], an organization independent of the OptimizeD trial team. The algorithm employs a maximum tolerated imbalance (MTI) procedure with a sliding window approach, incorporating a random element to minimize allocation predictability [56, 57]. This dynamic method balances key prognostic factors (clinic, sex, and PHQ-9 score dichotomized as <15 or ≥ 15) while reducing determinism in treatment assignment. Participants are allocated using CHaRT's online software, with the Trial Manager overseeing enrolment per assignment.

Although the main purpose of the trial is to compare optimal vs. non-optimal treatment rather than HAP vs. ADM, the outcome assessors will remain blinded to treatment allocation to improve methodological rigor. Participants and treatment providers are aware of treatment allocation, but participants are asked not to disclose their treatment to assessors. If an outcome assessor is unintentionally unblinded, the participant will be reassigned to another blinded assessor, and the incident will be documented for sensitivity analysis. Assessments are conducted at the participants' homes, clinics, by phone, or at a convenient location (e.g., parks, temples).

Interventions

Healthy Activity Program (HAP)

HAP is a brief, psychological treatment based on behavioral activation, an empirically supported treatment recommended by the WHO [11]. HAP incorporates strategies such as problem-solving, assertiveness training, and activation of social networks in a person-centered way. In our original HAP trial, 64% of participants with moderately severe to severe depression achieved remission (PHQ score <10) at 3 months, compared to 39% in the control group receiving enhanced usual care [41]. These benefits were sustained at 12 months [42].

HAP is delivered over 6–8 sessions over a 3-month period by trained counselors with undergraduate/graduate degrees in psychology, social work, or other related fields, but without prior counseling experience. HAP is delivered in an individual format, with each session lasting approximately 30–40 min. Sessions are conducted face-to-face, at the participant's home, or at a convenient location of the participant's choosing. If in-person sessions are not feasible, these may be conducted by phone.

HAP is a manualized treatment that is structured into three phases: (1) *Beginning phase (1–2 sessions):* Introduction to treatment, fostering hope, and building rapport; (2) *Middle phase (3–6 sessions)*: Core intervention strategies, including activation, problem-solving, and assertiveness skills, with relapse prevention as needed. Additional sessions (up to two) may be added for patients

Table 2 Schedule of assessments

				Study period					
Assessment	Screen	Baseline	Allocation	Acute treatment			Follow-up		
TIME POINT (W: weeks; M: months) **Location**	$-t_2$ Clinic	$-t_1$ Clinic	0 Clinic	1.5W Clinic /home/ phone	6W Clinic /home/ phone	12W Clinic / home	6M Clinic /home/ phone	9M Clinic /home/ phone	12M Clinic /home/ phone
SCREENING									
Eligibility screen	X								
Informed consent	X								
Allocation			X						
INTERVENTION & PROCESS INDICATORS									
HAP treatment [n=750] *Process indicators*: HAP session information (sessions completed, homework completed); Therapist outcomes (supervision quality, counselors quality ratings, fidelity assessor's rating, etc.)			●	———	———	●			
ADM treatment [n=750] *Process indicators:* Pill counts, appointment attendance, side effects, Adverse Reactions *(dashed line: continuation phase)*			●	———	———	●	- - -	- - -	●
ASSESSMENTS									
Depressive symptoms (PHQ9) *[Primary outcome]*	X			X	X	X	X	X	X
Baseline assessment**:** survey tools, neurocognitive tasks, blood sample (list of measures in Table A2 in the appendix).		X							
Mediator assessment: Anhedonia (SHAPS), Patient's activation (PAAS), Rumination (ARQ), Anxiety (GAD7), Loneliness (UCLA), Sleep (BPSQI)		X		X	X	X			X
Post-intervention assessment: same as baseline (except demographic questionnaire and prognostic constructs) and patient-rated change.						X			
Follow-up assessment: Depressive symptoms (PHQ-9), Wellbeing (WHO-5), Anxiety (GAD7), Disability (WHODAS-II). At 12-months we will include the CSRI and mediators.		X					X	X	X

ADM Antidepressant Medication, *ARQ* Analytical Rumination Questionnaire, *BPSQI* Brief Pittsburgh Sleep Quality Index, *CSRI* Client Service Receipt Inventory, *GAD-7* Generalized Anxiety Disorder-7, *HAP* Healthy Activity Program, *M* Months, *PAAS* Patient Activation Abbreviated Scale, *PHQ-9* Patient Health Questionnaire-9, *SHAPS* Snaith-Hamilton Pleasure Scale, *UCLA* UCLA Loneliness Scale, *W* Weeks, *WHO-5* World Health Organization Wellbeing Index, *WHODAS-II* World Health Organization Disability Assessment Schedule-II

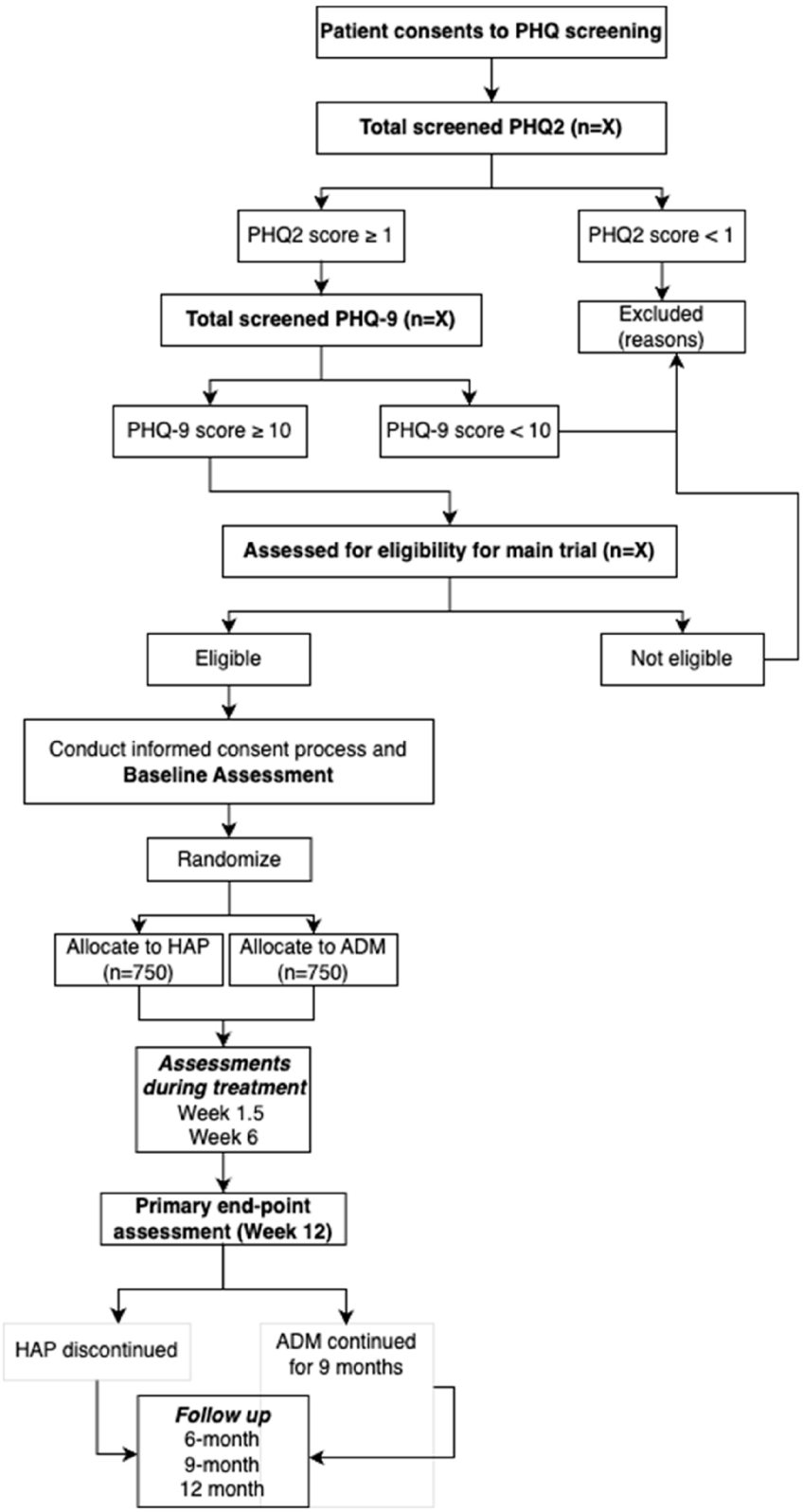

Fig. 1 Trial schema

with persistently high PHQ-9 scores (PHQ ≥ 10) and limited activation (measured by the number of homework assignments completed); and (3) *Ending phase (1 session):* Reviewing gains, consolidating skills, and preparing for termination. Each of these phases is characterized by specific goals and activities collaboratively agreed upon by the counselor and participant. The number of sessions may vary between 6 and 8, contingent upon the patient's symptomatic response (as indicated by PHQ-9 scores). Patients who achieve a PHQ-9 score ≤ 5 in sessions 3 or 4 and express interest in discharge may be considered for early termination after the 4th session, following a review with the HAP team leader. Further details of HAP can be found in the HAP manual [58].

Antidepressant medication (ADM)

Participants in the ADM group will receive fluoxetine, a selective serotonin reuptake inhibitor (SSRI) widely recognized for its safety and efficacy in treating depression [59]. Fluoxetine is part of India's Essential Drug List [60] and has demonstrated effectiveness in primary care [61]. A placebo-controlled trial in India reported a remission rate of 70% at 2 months among patients treated with fluoxetine, compared to 54% in the placebo group [61], which is notably higher than the range typically observed in meta-analyses [59].

The acute treatment phase will be delivered for 3 months, with clinicians conducting follow-up sessions at weeks 3, 6, and 12 to assess tolerability and symptoms and determine dosage adjustments. Participants will start at a dose of 20 mg per day and can be escalated to higher doses (40 mg) at subsequent visits, depending on tolerability and symptoms. The dose may be dropped to 10 mg daily if side effects occur.

During the continuation phase (months 4–12), the dose will be maintained based on PHQ-9 scores and tolerability, with adjustments made in consultation with the Medical Officer or the trial psychiatrist. At the 12-month visit, participants on doses higher than 20 mg/day will have their dose tapered to 20 mg/day for two weeks before discontinuation, while those on 20 mg/day will discontinue directly.

If fluoxetine is not tolerated, clinicians may switch participants to escitalopram at week 6, another SSRI recognized for its safety and efficacy, and also included in India's National List of Essential Medications [60, 62]. Escitalopram treatment will be initiated at 10 mg per day, with the option to increase to 20 mg daily based on tolerance and treatment response. These participants will undergo an additional follow-up session at week 9 to monitor progress.

If a participant experiences a serious side effect from taking fluoxetine or escitalopram, they will be referred to specialist care. Outcome data for participants switched to escitalopram or referred to specialist care will continue to be collected, and we will conduct sensitivity analyses to assess the impact of these treatment modifications on primary and secondary outcomes.

Medical Officers from the recruiting clinics are the primary healthcare providers prescribing medication in OptimizeD. In situations in which the Medical Officer is not available, the trial psychiatrist has been authorized by the state health system to prescribe medication via telemedicine. Both fluoxetine and escitalopram are provided free of charge to participants through government supply channels.

Quality and fidelity of the intervention

HAP HAP counselors participate in weekly group supervision and monthly individual supervision to review audio-recorded sessions, practice role-plays, and address patient-specific challenges. Group supervision, facilitated by a HAP supervisor, is conducted in peer groups of 5–6 counselors, while individual supervision, led by the HAP team leader, provides more in-depth, one-on-one guidance.

We assess HAP quality using the following metrics:

- *Participants' adherence to HAP treatment.* We will explore several indicators, such as treatment dose (measured by the number of sessions completed) and homework engagement. Treatment compliance will be defined as attending at least six sessions or requesting discharge after four sessions with PHQ-9 scores below 5 in both the third and fourth sessions.
- *Therapy quality.* We will assess the quality of two agents:

  - Quality of HAP counselors: Assessed through the rating of audio-taped sessions using a specifically developed scale called the Quality of Behavioral Activation Scale (Q-BAS), a 20-item, 5-point Likert scale [63, 64]. Higher scores indicate higher implementation quality. Weekly supervision sessions include independent ratings of audio-recorded sessions by the counselor, their peers, and the supervisor, with aggregate scores calculated for each group.
  - Quality of the HAP supervisor: Assessed using the EMPOWERS rating scale (a five-point Likert scale with 8 items that assesses the skills required to facilitate supervision sessions) [64]. At the end of the session, all the HAP counselors and the HAP super-

visor will rate the facilitation quality of the session. Aggregate scores of all counselors and the supervisor will be evaluated.

We will assess HAP fidelity using the following approach:

- *External fidelity rating.* Independent experts, unaffiliated with the OptimizeD trial but previously involved in HAP development or delivery, will randomly evaluate and rate 5% of all audio-recorded HAP sessions, stratified by counselor and treatment phase. Each week, the same audio-recorded sessions that are rated by counselors and the supervisor are also assessed by fidelity assessors to ensure consistency in scoring.

ADM We will assess ADM quality using the following metrics:

- *Participants' ADM adherence.* We will explore several indicators, such as appointment attendance and dose adherence. Pill counts will be conducted at regular intervals to measure medication adherence. At each visit, participants will receive three sequentially numbered blister packs, each containing 10 pills. Participants will be asked to retain any empty blisters of medications and hand them over to the research staff at the next visit. The number of blisters and pills returned will be counted and recorded. To calculate adherence, we will sum the total number of pills and divide it by the days in treatment.
- *Quality of ADM delivery.* We will assess the following indicators:
  - Medication dispensation: We will assess the fidelity of antidepressant delivery by monitoring the accurate dispensation of medications to participants by RAs. This will involve tracking the prescription and distribution of antidepressant medications according to established treatment protocols.
  - Medical Officer training: We will measure whether the Medical Officer attended the training on the OptimizeD trial and clinical protocol.
  - Adverse event monitoring: Adverse events or side effects experienced by participants while taking antidepressant medications will be monitored and reported, ensuring they are appropriately managed.

Unlike psychotherapy interventions, for which external ratings by independent experts are commonly employed as a measure of fidelity, administering antidepressant medications does not lend itself to this type of external rating. Instead, we will focus on assessing the quality of ADM delivery to ensure the safe and effective administration of medication within the study.

Strategies to improve treatment adherence

Several strategies will be employed to enhance treatment completion rates, drawing on our experience with previous studies in the setting [41, 61, 65]. First, participants will receive thorough education about their treatment before providing consent, including the purpose, potential benefits, and possible side effects of each intervention. Second, Medical Officers will play a key role in reinforcing treatment adherence. Third, and to ensure continuity of care, the trial psychiatrist is authorized by the state health system to prescribe antidepressant medications via telemedicine in cases where the Medical Officer is unavailable. Fourth, HAP sessions will be delivered flexibly, with options for participants to attend sessions at clinics, their homes, or other preferred locations. The HAP counselors will accommodate participants' schedules, including after-work hours and weekends, and offer telephonic sessions for those uncomfortable with in-person meetings. Fifth, medications will be delivered to participants' homes or other convenient locations whenever they are unable to visit the clinic, minimizing logistical barriers. Sixth, family involvement will also be encouraged, with participant consent, to provide additional support for treatment adherence. Seventh, reminder calls will be made 48 h before scheduled treatment sessions, followed by text message reminders 24 h prior. If participants miss a scheduled session, the research team will reach out to determine the reason and reschedule to maintain engagement and continuity in the treatment process. These strategies collectively aim to reduce barriers to adherence and enhance treatment outcomes.

Criteria for discontinuing or modifying allocated interventions

There are several circumstances that might result in a participant discontinuing treatment, as outlined in Table 3. If a participant discontinues HAP or ADM, we will nonetheless attempt to keep them in the study in terms of completing follow-up assessments.

Table 3 Conditions and procedures for discontinuation or adjustment of trial interventions

Condition	Assessment	Action
Any participant experiencing an acute psychiatric episode that may compromise their well-being or the integrity of the study	Clinical evaluation by the OptimizeD clinical team	The participant will be excluded from the treatment for their safety and referred for appropriate psychiatric care at AIIMS Bhopal
Intolerance to both ADMs (fluoxetine and escitalopram) or a serious adverse reaction	ADM intolerance will be assessed using the Antidepressant Side Effect Checklist (ASEC) and Medical Officers clinical evaluation	Participants experiencing ADM intolerance to fluoxetine and escitalopram will be excluded from the treatment for their safety and referred to AIIMS Bhopal
Conflicts with the HAP counselor	This may be determined by the supervisor of the concerned HAP counselor	All efforts will be made to change the HAP counselor, if available. If the participant chooses to discontinue, reasons will be documented
Participant's voluntary discontinuation	Participants choosing to discontinue will be encouraged to provide reasons for their decision through open communication	Efforts will be made to address their concerns, provide necessary information, and motivate them to reconsider treatment continuation. Their reasons will be documented. Participants who still wish to discontinue will be allowed to do so, in accordance with ethical guidelines for trial participation

Participant discontinuation/withdrawal

Participants may withdraw from the study at any time upon request. Additionally, investigators may discontinue participants due to being lost to follow-up or if a medical condition arises that could compromise participant safety. For participants who become pregnant, those in the HAP arm will continue their sessions without modification, while those in the ADM arm will undergo a treatment review with the clinical team to reassess medication safety and adjust the treatment plan as needed. Withdrawal reasons will be recorded, and once randomized, participants will not be replaced. Lost-to-follow-up will be determined after three unsuccessful contact attempts, including phone calls and a home visit, with all contact attempts documented. Participants who explicitly choose to withdraw or remain unreachable after these attempts will be classified as withdrawn. Participants who wish to rejoin the study may resume from their original enrollment point.

Strategies to improve adherence to study assessments

Several strategies will be employed to promote adherence to research assessments. First, participants will receive clear information about the study's time commitments before enrollment to ensure informed consent. Second, Medical Officers will encourage participation at study onset and will intervene if non-adherence is observed. Third, surveys will be divided into shorter segments to reduce participant burden, with breaks included to maintain engagement. Fourth, while participants do not receive direct payment for participation, they will receive 500 Indian Rupees (INR) for each of the seven scheduled assessments, totaling 3,500 INR (approximately USD 40). Fifth, reminder calls and text messages will be sent 48 and 24 h before each scheduled study assessment to minimize missed visits. Finally, if a participant misses a scheduled session, the research team will contact them to identify and address barriers, rescheduling the session as needed.

Relevant concomitant care permitted or prohibited during the trial

Participants receiving any treatments for depression (psychological or pharmacological) at the start of the trial or within one month prior to recruitment will not be eligible for participation. Participants may use analgesics for pain control, including over-the-counter medications such as non-steroidal anti-inflammatory drugs (e.g., ibuprofen, aspirin) and paracetamol, as well as prescribed medications for conditions other than depression. Medication usage will be assessed at baseline, 3-month, and 12-month study assessments.

Provisions for post-trial care

At the 12-month assessment, which marks the final study assessment, participants will be briefed on their current symptom levels of depression. Those with PHQ-9 scores ≥ 10, as well as those scoring between 5–9 who show less than 50% symptom improvement from baseline, will be offered the option of being referred to specialist care at the collaborating tertiary care institute – the All India Institute of Medical Sciences (AIIMS Bhopal) for further mental health support services.

Sample size

This study is designed to provide sufficient power to generate and validate the PTR to predict differential responses to HAP versus ADM (primary objective 1). A total of 1,500 participants will be randomized to either HAP or ADM. Of these, the first 1,000 participants will be used to train the PTR algorithm, using cross-validation for hyperparameter tuning and nested cross-validation for calibration, while the remaining 500 participants will form an independent validation sample to evaluate the algorithm's predictive accuracy. The sample size required for generating a valid PTR depends on the anticipated attained marginal improvement (AMI), which quantifies the additional benefit of assigning patients to their optimal treatment compared to the intervention with the larger average treatment effect. Power calculations based on simulations using realistic assumptions about underlying processes generating the AMIs suggest that 300–500 patients per arm (600–1,000 total) are required to detect AMIs in the range from 5% (minimal improvement) to 25% (substantial improvement) with statistical power of at least 0.8 using two-sided $p = 0.05$ significance tests [36]. Our trial, with 750 participants per arm, will consequently be well powered to develop a useful PTR if meaningful heterogeneity exists in differential treatment response and our baseline covariates are sufficiently predictive to find AMI in this range. The economic analyses (primary objective 2) will utilize the full sample of 1,500 participants. This ensures adequate power to perform cost-effectiveness comparisons between HAP and ADM.

While mediation analyses (exploratory objective 1) are not the primary focus of the sample size determination, the total sample size of 1,500 is approximately three times larger than the 500 participants typically needed to detect mediation effects with adequate power [66]. However, detecting moderated mediation effects is more challenging, often requiring four times the sample size used for standard mediation analyses [67]. Applying this rule of thumb, our sample size of 1,500 aligns with the recommended threshold for detecting moderated mediation effects, though power will depend on the effect sizes of

both the direct and indirect effects [68]. The genetic analyses (exploratory objective 2) are intended to be exploratory, with power calculations currently premature, particularly in a cross-ancestry context. These analyses will explore whether integrating polygenic risk scores and other genetic and biological biomarkers can enhance the predictive utility of the PTR.

In summary, this study is powered to generate and test a robust PTR (primary objective 1), conduct adequately powered economic analyses (primary objective 2), and provide exploratory insights into mediation and genetic moderators to guide future research.

Data management

Data will be primarily collected using REDCap [54] via tablets and uploaded daily to Sangath's secure server. Neurocognitive tasks will be administered via tablets using NubiS, a software designed for complex cognitive assessments [69]. HAP-related data will be collected using the PEERS app, a smartphone-based system built on the CommCare platform [70]. For participants in the ADM arm, pill counts will be recorded on paper and entered into RedCap. Additionally, audio recordings of surveys will be collected from participants who consent to this component to facilitate data quality checks. Paper-based documents, such as signed consent forms and patient cards, will be securely stored in locked filing cabinets at the Sangath Bhopal office. Data will be regularly backed up, de-identified, cleaned, and stored securely for a minimum of seven years post study completion. All identifiable information will be stored separately from the research data, and participants will be identified in study files only by their unique study ID.

The team at AIIMS Bhopal will manage the processing of the biological samples. Samples will be stored in temperature-controlled, access-restricted facilities and labeled with study IDs only. De-identified genetic data will be transferred via secure, encrypted channels to Harvard/Massachusetts General Hospital for analysis. Biospecimens will be retained in accordance with local regulations and participant consent.

Statistical analysis

Precision treatment rule (PTR)

We aim to develop a precision treatment rule (PTR) to identify the optimal treatment for each patient by modeling how baseline characteristics interact with treatment type to predict outcomes. This will involve estimating predicted outcomes for each patient under both treatment conditions (HAP and ADM) and calculating an individual-level difference score to identify optimal treatment assignment.

Traditional regression-based PTR models typically rely on correctly specifying main effects and simple two-way interactions, where treatment effects vary based on specific baseline characteristics but do not account for more complex interaction patterns [71]. For example, treatment effects might be modeled as a function of treatment assignment (T), gender (G), and baseline depression severity (BDS) as follows:

$$\text{Outcome} = b_0 + b_1 T + b_2 G + b_3 \text{BDS} + b_4 (T \times G) + b_5 (T \times \text{BDS}),$$

However, interactions can be far more complex, involving nonlinearities and higher-order effects. For example, the differential effect of treatments A and B among women compared to men might only be present at specific levels of baseline depression severity. To account for these complexities, we will use a more flexible and robust machine learning approach that estimates interactions based on counterfactual logic. In this approach, prediction models are estimated separately within each treatment arm, assigning each patient two predicted outcome scores (one for HAP and one for ADM) based on baseline covariates. These scores represent the expected outcome under each treatment, allowing us to estimate how much a patient's outcome would differ if they had been assigned to one treatment versus the other. This difference is known as the conditional average treatment effect (CATE).

The within-arm models will be estimated using the Super Learner (SL) algorithm, an ensemble machine learning method that allows for both nonlinearities and higher-order interactions [72]. The optimal combination of algorithms is defined based on an objective function, which in our case will be maximum reduction in cross-validated mean-squared error in the outcome. SL improves accuracy and reduces the risk of model misspecification [73]. Our SL library will include a range of modern machine learning algorithms such as penalized regression, tree-based methods, support vector machines, and gradient boosting. Importantly, preliminary models will be estimated in a nested cross-validation framework to predict differential engagement with HAP and differential adherence to ADM. This step allows us to create composite predictors to determine the extent to which the PTR is predicting differential engagement/adherence versus differential intervention effectiveness [74].

Once the within-arm prediction models are created, we will assign predicted probabilities to each patient based on each equation. Since the two subsamples of patients are equivalent by design, both equations should apply to both subsamples. The difference between these two predicted scores at the individual level will represent

the estimated CATE, indicating the expected impact of assigning a patient to HAP versus ADM.

These initial CATE estimates will be used as the outcome in a second SL ensemble analysis to identify baseline predictors of treatment effect differences. Unlike traditional approaches, this method does not require accurate specification of main effects because composite interactions – represented by CATEs – are being directly estimated by pooling estimates across algorithms in the ensemble. Doubly robust methods will be applied in this analysis to adjust for potential loss to follow-up.

If CATE estimates differ significantly across patients, with some estimates favoring HAP and others favoring ADM, we will use nested cross-validation to estimate the expected improvement in aggregate outcomes if patients were assigned to treatments based on their estimated CATEs rather than at random. Additionally, if one treatment is found to be superior overall, we will also estimate the expected improvement in aggregate outcomes if patients were assigned to treatments based on their estimated CATEs rather than assigning all patients to the treatment with the best average effect.

A key challenge in using complex machine learning methods is the risk of overfitting, which can degrade model performance when the model is applied elsewhere. To address this, we will implement several strategies. First, we will exclude potential predictors with fewer than 10 observations in the smaller cell of a dichotomous variable. Second, we will use cross-validation to assess whether potential predictors have stable, significant univariable associations with the outcome. Third, associations among potential predictors that pass the second test will be examined, and only predictors with correlations of $r \geq 0.80$ will be retained in the final predictor set. Fourth, potential predictor screening and restriction will be used at the analysis stage to avoid overfitting by allowing only 5%, 10%, or 20% as many predictors in the model as we have patients with outcomes to predict. Selection of this restricted number of predictors will be carried out using Lasso penalized regression for linear algorithms and random forest for more complex algorithms. A separate selection procedure will be used for each fold in the tenfold cross-validation used to estimate models. Fifth, each classifier will be included in the ensemble multiple times, each time with a distinct set of hyperparameter values selected at random across a multivariable grid of key features. The SL weighting procedure will then be used to select the optimal hyperparameter configuration to include in the ensemble. Lastly, the final SL ensemble will consist of three times the number of classifiers, each estimated with distinct predictor sets within each cross-validation fold.

Cost-effectiveness analysis

Our economic evaluation will assess the cost-effectiveness of using a PTR to guide depression treatment by comparing the costs and outcomes of optimal versus non-optimal treatment assignments. We will examine (1) total costs and cost per remission or recovery for each group; (2) the cost-effectiveness of random assignment to optimal vs. non-optimal treatment; and (3) how cost-effectiveness varies across different levels of predicted probability of remission and recovery from the PTR. We hypothesize that optimal treatment will be more cost-effective than non-optimal treatment in achieving remission or recovery, and that cost-effectiveness will increase with greater predicted benefit, as indicated by higher PTR differential scores.

Costs will be assessed from both the health system and societal perspectives, including direct, indirect, and opportunity costs. System-level costs will be estimated using instruments based on the WHO health systems building blocks framework, [75, 76] capturing resources used for ADM and HAP training and delivery, biological collection and analysis, and PTR measurement. Cost components will include staff time, infrastructure, equipment, and unpaid contributions. Patient-level costs will include the costs of participating in treatment, such as transportation and lost wages, captured with a tailored 7-item tool. We will also collect participants' out-of-pocket and non-medical costs data of obtaining general care using the Client Service Receipt Inventory (CSRI) [77]. The CSRI data will allow us to (1) examine the difference in changes of household economic burden resulting from receiving general care between the optimized and non-optimized groups, and (2) estimate the difference in savings at the health system level resulting from treating depression using optimized versus non-optimized methods. Effectiveness will be measured by (1) the likelihood of remission and recovery (using multilevel logistic regression) and (2) quality-adjusted life years (QALYs), derived from WHODAS-II scores. Incremental costs and incremental effectiveness will be derived using the multilevel generalized linear models. All models will adjust for clustering at the clinic level.

We will obtain the mean and 95% confidence intervals of the incremental cost-effectiveness ratios using the bootstrapping method [78, 79]. Cost-effectiveness acceptability curves will be produced across a range of willingness-to-pay thresholds from either a health system perspective or a societal perspective. Finally, we will explore the added value of the PTR by conducting

separate analyses for remission and recovery, stratifying participants assigned to their optimal treatment into four groups based on the predicted probability of each outcome (< 25%, 25–50%, 51–75%, > 75%). This allows us to test whether cost-effectiveness varies with the strength of the PTR recommendation, offering practical guidance for decision-makers on when optimization yields the highest value.

Mediation analysis

Mediation analyses will be conducted using MPlus (version 8.4 or higher) or any other appropriate statistical analysis packages. We will estimate the indirect effects of the proposed mediators on remission and recovery.

We will begin by examining each mediator independently, followed by simultaneous testing of multiple mediators using the Monte Carlo Method for Assessing Mediation. Indirect effects will be estimated as the product of two normally distributed coefficients, and MPlus will be used to simulate the distribution and calculate asymmetric 95% confidence intervals (based on 20,000 repetitions). For analyses involving multiple mediators, we will apply methods from causal mediation analysis to estimate effects through all mediators jointly, modeling both the outcome on all mediators and each mediator separately while adjusting for baseline covariates to control for confounding [80].

Biological specimen analysis

At baseline assessment, 5 mL of peripheral blood or 1 mL of saliva will be collected by trained personnel from each consenting participant during their baseline visit. Samples will be transported securely to AIIMS Bhopal and processed for genomic DNA extraction using the QIAamp DNA Blood Kit [81]. DNA quantification will be conducted using the Qubit™ Fluorometer [82] with the High Sensitivity (HS) Assay Kit. DNA integrity will be assessed by agarose gel electrophoresis. Purity and concentration will be further confirmed by measuring the 260/280 absorbance ratio (1.8–2.0) using a NanoDrop™ spectrophotometer [83, 84].

Genome-wide genotyping will be performed using the Illumina™ Global Screening Array (GSA), a high-throughput genotyping platform. It employs BeadChip technology and includes more than 650,000 variants across diverse populations, providing coverage of disease-associated and pharmacogenomic markers, and high-value exonic variants [85].

We will apply standard genomic quality control and imputation procedures, applicable across population backgrounds. Broadly, variants will be filtered based on sample missingness and other quality control criteria, and individuals will also be filtered based on genotype missingness. We will conduct ancestry assignment based on principal components projected against the 1000 Genomes Project reference panel, followed by additional quality control measures (e.g., for sex mismatch or heterozygosity) within ancestry groups. Imputation will be conducted using standard imputation platforms (e.g., TopMED). Following imputation, additional quality checks will be applied, including the removal of variants with low imputation accuracy and filtering for minor allele frequency and violations of Hardy–Weinberg equilibrium.

Polygenic risk scores Polygenic risk scores (PRS) will be calculated as the weighted sum of allele dosages across variants combined with per-variant effects from summary statistics from prior large-scale genome-wide association (GWAS) studies [86]. We will generate polygenic scores for major depressive disorder, other psychiatric disorders (e.g., schizophrenia, bipolar disorder, ASD), personality traits (e.g., neuroticism), and cognitive function, in line with existing studies on genetics and treatment response. To improve predictive accuracy, particularly across ancestries, we will use PRS continuous shrinkage (PRS-CS), a Bayesian polygenic scoring method that accounts for linkage disequilibrium using relevant (e.g., South Asian) reference panels from the 1000 Genomes Project [87]. PRS-CS has shown superior performance over traditional methods, especially in non-European populations. As methods for optimizing cross-ancestry PRS performance evolve, we will incorporate new approaches as appropriate [88]. Using the generated PGS, we will then examine associations between each PRS and PHQ-9 scores at baseline, 12 weeks, and 12 months, as well as remission and recovery, adjusting for principal components, age, and sex. We will also assess whether the inclusion of PRS data improves the predictive accuracy of the personalized treatment rule (PTR) models in identifying optimal treatment assignments.

Pharmacogenomic analysis CYP2D6 genotyping and metabolizer status analysis will be conducted using TaqMan® CNV [89] and SNP genotyping assays, targeting clinically relevant CYP2D6 alleles. We will determine each participant's metabolizer phenotype as a potential predictor of fluoxetine response. In addition to examining the independent predictive value of CYP2D6 status, we will also assess whether integrating pharmacogenomic data into the PTR models, alongside PRS, improves treatment prediction accuracy.

Table 4 Study management and committees

Committee	Role	Composition	Frequency of meeting
Project Management Committee (PMC)	The PMC will monitor all aspects of the conduct and progress of the project, ensure that the protocol is adhered to, and take appropriate action to manage any deviations	Chaired by the site-PI Bhan and will be comprised of the following: the trial manager, project coordinators, data team, and co-Is coordinating specific thematic areas	The PMC will meet weekly until 50% of the target sample has been enrolled, and will shift to biweekly meetings thereafter
Trial Steering Committee (TSC)	The TSC will be the primary decision-making body on policy matters including resource management and will provide oversight of the project to ensure it is conducted in accordance with the protocol and the relevant regulations and milestones are being met in a timely manner. The TSC is the final body to approve the trial protocol and any amendments	Chaired by the two PIs in rotation and include the site-PIs, co-Is, trial manager, and project coordinators	The TSC will meet monthly
Data and Safety Monitoring Board (DSMB)	Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including clinical trial methodology, biostatistics, mental health research, and research ethics	The members of the DSMB for the OptimizeD trial are: *1) Professor Charles F. Reynolds III, MD.* [Chair] UPMC Endowed Professor in Geriatric Psychiatry at the University of Pittsburgh School of Medicine and Professor of Behavioral and Community Health Sciences at the Graduate School of Public Health; and an expert in clinical trial methodology; 2) *Professor Stephen Wisniewski*. Vice Provost and Professor of Epidemiology at the University of Pittsburgh; and an expert in the field of biostatistics; 3) *Professor Claudi Bockting.* Professor of Clinical Psychology in Psychiatry at Amsterdam University Medical Centers); and an expert in the field of mental health research; 4) *Professor Smita N Deshpande.* Professor of Psychiatry at St John's National Academy of Health Sciences, Bengaluru; and an expert in psychiatric genetics and research ethics. 5) *Mr. Anantha Narayana Agasthya.* Caregiver for over 25 years; Lived experience expertise; Member of Executive Committee of AMEND; Expert in Quality and Operations Management. Members of the DSMB will be independent from the study conduct and free of conflict of interest	The DSMB will meet twice yearly to monitor the trial conduct.

Additional exploratory analyses

- *C-Reactive Protein (CRP) measurement*: CRP concentration will be measured in the serum CRP CardioPhase® HS Assay Kit [90] to evaluate the role of systemic inflammation in influencing therapeutic outcomes.
- *Pharmacogenomic Variant Analysis:* We will examine the prevalence of SNPs and CNVs in Tier 1 pharmacogenes (*CYP2D6, CYP2 C19, CYP2B6*) related to antidepressants in our central Indian sample and compare them to other Indian and international populations and possible clinical implications.
- *Cross-platform concordance:* As *CYP2D6* CNVs will be assessed using both microarray-based (Global Screening Array) and TaqMan-based genotyping methods, we will evaluate concordance between the two technologies in detecting CNVs.
- *Comparison of DNA Sources:* We will compare genotyping efficiency and quality metrics between saliva-derived and blood-derived DNA samples to assess feasibility for future large-scale studies.

Oversight and management

The PIs will have overall responsibility for monitoring the integrity of study data and participant safety. In addition, several trial committees have been established to oversee participant safety and data quality, including a Project Management Committee, a Trial Steering Committee, and a Data and Safety Monitoring Board (DSMB). Details about the roles and composition of these committees are provided in Table 4.

Serious adverse events

We define a Serious Adverse Event (SAE) as any adverse event that results in death, is life-threatening, requires hospitalization, causes significant disability, or may jeopardize health and require medical intervention. All SAEs will be assessed for relatedness to study procedures and expectedness by the clinical team. SAEs may be reported during study or intervention visits or via disclosure to research personnel.

SAEs will be compiled by the Trial Manager and shared with the PIs, relevant co-Is, and the Trial Psychiatrist. All SAEs—regardless of relatedness—will be reported to the Sangath IRB within 24 h of becoming known to the study team. Only SAEs determined to be related to study procedures will be reported to the AIIMS IRB, HMS IRB, the NIMH Program Officer, and the DSMB Chair within two business days of awareness by the Principal Investigators. The Trial Psychiatrist will conduct a follow-up assessment within five business days of the report, and a detailed assessment will be submitted to relevant IRBs and NIMH within 14 days. These procedures are aligned with India's research ethics guidelines to ensure participant safety and regulatory compliance.

Discussion

Depression represents a significant global health challenge characterized by substantial heterogeneity in treatment response [16–19]. This variability presents a critical obstacle for clinicians, particularly in primary care settings with limited resources. Conventional approaches rely on sequential, trial-and-error strategies that often delay remission and increase the risk of chronicity [16, 91]. In contexts where accessing treatment is difficult, such stepped-care approaches become impractical. This reality underscores the urgent need to optimize initial treatment selection to improve early outcomes and make the most of limited mental health resources.

The OptimizeD trial aims to address this challenge by developing and validating a pragmatic, precision-guided approach to first-line depression treatment in primary care. By using data that can be feasibly collected in routine practice, the study aims to improve the efficiency and impact of care without relying on specialized technologies or settings. The study's methodological strengths—including its large sample size, rigorous design, long-term follow-up, and diverse, scalable set of candidate moderators informing the PTR—improve the potential for generating findings that are both robust and implementable in real-world settings.

Beyond its methodological contributions, the findings from this study may offer practical insights for health system planning and resource allocation. Our cost-effectiveness analyses will assess whether optimizing treatment selection can improve efficiency by directing resources where they are most likely to help. By stratifying participants according to their predicted likelihood of remission, the findings could inform tiered implementation strategies that match intervention intensity to patient needs [92]. Moreover, identifying probable non-responders to first-line treatment could support timelier referral to specialist care and improve continuity of services.

If successful, the findings from OptimizeD will demonstrate the feasibility of integrating precision approaches into routine mental health care in low-resource settings. It offers a unique opportunity to test whether data-driven treatment selection can both improve patient outcomes and make more efficient use of limited resources. Ultimately, the findings could potentially shift global mental healthcare toward a more adaptive, person-centered model that aligns treatment with individual needs.

Trial status

Trial recruitment started on 18 March 2024. Recruitment is tentatively scheduled to be completed in December 2025.

Abbreviations

ADM	Antidepressant medication
AIIMS	All India Institute of Medical Sciences
AMI	Attained marginal improvement
CATE	Conditional average treatment effect
CNV	Copy number variation
C-SSRS	Columbia Suicide Severity Rating Scale
CSRI	Client Service Receipt Inventory
DSMB	Data and Safety Monitoring Board
GSA	Global Screening Array
GWAS	Genome-wide association study
HAP	Healthy Activity Program
HS	High Sensitivity
IRB	Institutional review board
MTI	Maximum tolerated imbalance
PHQ-9	Patient Health Questionnaire-9
PRS	Polygenic risk score
PRS-CS	Polygenic risk score continuous shrinkage
PTR	Precision treatment rule
REDCap	Research Electronic Data Capture
SAE	Serious adverse event
SL	Super learner
SNP	Single nucleotide polymorphism
SSRI	Selective serotonin reuptake inhibitor
WHO	World Health Organization
WHODAS-II	World Health Organization Disability Assessment Schedule-II

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-07030-9.

Supplementary Material 1.

Acknowledgements

We thank all the participants who generously took part in the study. We are also grateful to the state health system – the National Health Mission (NHM) Madhya Pradesh, the Mission Director (NHM Madhya Pradesh), the Chief Medical and Health Officer (CMHO) Bhopal, Assistant Program Manager (CMHO Bhopal office), Data Entry Operator (CMHO Bhopal office), the Medical Officers and other staff working in primary healthcare facilities, and the psychological treatment providers for their ongoing support. We also thank all the support staff across the collaborating institutions who enable the study to be conducted. Finally, we are grateful for the research staff whose dedication enables the daily implementation of the OptimizeD trial.

Author's contributions

JRP drafted the initial manuscript. All authors reviewed the manuscript and approved the final submission. Funding acquisition was led by VP, SDH, DRS, CL, PC, RDR, RCK, MH, AB, JAN, JWS, KC, AR, UK, AK, and TJV. All members of the Trial Steering Committee (TSC) contributed to the methodology and implementation of the trial. JRP, SDH, and RCK led the selection of study measures, with input from members of the TSC. AL, RS, AK, MK, YM, and AB were responsible for participant recruitment and study follow-up. Risk management procedures were coordinated by AL, MMJ, JRP, AR, TM, AN, SDH, and VP. JRP, SG, VS, and YP managed data collection and quality control. AK, AK, RS, and YM led the clinical workstream, with supervisory input from TSC members. RCK led the development and analysis of the precision treatment rule workstream. CL and JRP led the economic evaluation workstream. DRS and TJV led the mediator analysis workstream. DB, SA, UK, JWS, and KWC led the genomics workstream. VP and SDH provided oversight and guidance throughout the study and are co-senior authors.

Funding

This trial is funded by the National Institute of Mental Health (R01MH121632), which underwent independent peer review as part of the funding approval process. The funder played no role in the study design, data collection, analysis, interpretation, manuscript writing, or submission for publication.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study is approved by the ethics committees of Harvard Medical School (IRB20-2144, v11), Sangath (AB-2021–69, v1.7), and AIIMS Bhopal (EF0237). Additional approval, as required for all foreign-funded research in India, was obtained from the Government of India's Health Ministry Screening Committee, housed at the Indian Council of Medical Research. Amendments to the protocol are agreed upon by the TSC and approved by relevant IRBs prior to implementation. The consent process, conducted by trained and supervised Research Assistants, includes three stages: consent for the screening/eligibility survey, consent for main study enrollment for eligible participants, and a separate consent for blood or saliva sample collection. To standardize the process and ensure consistent delivery of key information, a video was developed to guide participants through the consent procedures. Written informed consent at each stage is mandatory for enrolling in the trial. While study participants do not receive direct payment for their participation, they receive 500 INR as reimbursement for the opportunity cost for each of the seven scheduled study assessments (baseline, week 1.5, week 6, week 12, month 6, month 9, and month 12), totaling 3,500 INR, approximately USD 40).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Global Health and Social Medicine, Harvard Medical School, 641 Huntington Avenue, Boston, MA 02115, USA. [2]Department of Psychiatry, University of Oxford, Oxford, United Kingdom. [3]MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. [4]Bhopal Hub, Sangath, Bhopal, India. [5]Department of Health Care Policy, Harvard Medical School, Boston, MA, USA. [6]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Canada. [7]Department of Psychiatry, Temerty Faculty of Medicine, University of Toronto, Toronto, Canada. [8]Lunenfeld-Tanenbaum Research Institute, Sinai Health, Toronto, Canada. [9]Department of Psychiatry, Center for Precision Psychiatry, Massachusetts General Hospital, Boston, MA, USA. [10]Psychiatric & Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA. [11]Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health Research Institute, Vrije Universiteit, Amsterdam, The Netherlands. [12]International Institute for Psychotherapy, Babeș-Bolyai University, Cluj-Napoca, Romania. [13]Department of Psychology, University of Pennsylvania, Philadelphia, PA, USA. [14]Palestinian Neuroscience Initiative, Al-Quds University, Jerusalem, Palestine. [15]Center for Molecular and Behavioral Neuroscience, Rutgers University, Newark, NJ, USA. [16]Division of Global Health Equity, Brigham & Women's Hospital, Boston, MA, USA. [17]Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA. [18]Harvard T.H. Chan School of Public Health, Boston, MA, USA. [19]All India Institute of Medical Sciences (AIIMS) Bhopal, Bhopal, India. [20]Department of Psychology, Vanderbilt University, Nashville, TN, USA.

Received: 21 May 2025 Accepted: 26 May 2025
Published online: 30 July 2025

References

1. McGrath JJ, Al-Hamzawi A, Alonso J, Altwaijri Y, Andrade LH, Bromet EJ, et al. Age of onset and cumulative risk of mental disorders: a cross-national analysis of population surveys from 29 countries. Lancet Psychiatry. 2023;10(9):668–81.
2. Ferrari AJ, Santomauro DF, Aali A, Abate YH, Abbafati C, Abbastabar H, et al. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. The Lancet. 2024;403(10440):2133–61.
3. Rathod S, Pinninti N, Irfan M, Gorczynski P, Rathod P, Gega L, et al. Mental health service provision in low- and middle-income countries. Health Serv Insights. 2017;28(10):1178632917694350.
4. Moitra M, Santomauro D, Collins PY, Vos T, Whiteford H, Saxena S, et al. The global gap in treatment coverage for major depressive disorder in 84 countries from 2000–2019: A systematic review and Bayesian meta-regression analysis. PLoS Med. 2022Feb 15;19(2):e1003901.
5. Fekadu A, Demissie M, Birhane R, Medhin G, Bitew T, Hailemariam M, et al. Under detection of depression in primary care settings in low and middle-income countries: a systematic review and meta-analysis. Syst Rev. 2022;11(1):21.
6. Lund C, Breen A, Flisher AJ, Kakuma R, Corrigall J, Joska JA, et al. Poverty and common mental disorders in low and middle income countries: A systematic review. Soc Sci Med. 2010;71(3):517–28.
7. Ridley M, Rao G, Schilbach F, Patel V. Poverty, depression, and anxiety: causal evidence and mechanisms. Science. 2020;370(6522):eaay0214.
8. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet. 2007;370(9590):851–8.
9. Kessler RC. The costs of depression. Psychiatr Clin North Am. 2012;35(1):1–14.
10. Patel V, Saxena S, Lund C, Thornicroft G, Baingana F, Bolton P, et al. The Lancet Commission on global mental health and sustainable development. Lancet. 2018;392(10157):1553–98.
11. WHO. mhGAPintervention guide for mental, neurological and substance use disorders in non- specialized health settings: mental health Gap Action Programme (mhGAP). Geneva: WHO; 2010. Available from: https://www.who.int/publications-detail-redirect/9789241549790. Cited 2023 Sep 3.
12. Patel V, Chisholm D, Parikh R, Charlson FJ, Degenhardt L, Dua T, et al. Addressing the burden of mental, neurological, and substance use disorders: key messages from Disease Control Priorities, 3rd edition. Lancet. 2016;387(10028):1672–85.
13. Cuijpers P, Noma H, Karyotaki E, Vinkers CH, Cipriani A, Furukawa TA. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. World Psychiatry. 2020;19(1):92–107.
14. Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds CF. The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: a meta-analysis of direct comparisons. World Psychiatry. 2013;12(2):137–48.
15. Cuijpers P. The challenges of improving treatments for depression. JAMA. 2018;320(24):2529–30.
16. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163(11):1905–17.
17. Kessler RC, van Loo HM, Wardenaar KJ, Bossarte RM, Brenner LA, Ebert DD, et al. Using patient self-reports to study heterogeneity of treatment effects in major depressive disorder. Epidemiol Psychiatr Sci. 2017;26(1):22–36.
18. Milaneschi Y, Lamers F, Berk M, Penninx BWJH. Depression heterogeneity and its biological underpinnings: toward immunometabolic depression. Biol Psychiatry. 2020;88(5):369–80.
19. Kaiser T, Volkmann C, Volkmann A, Karyotaki E, Cuijpers P, Brakemeier EL. Heterogeneity of treatment effects in trials on psychotherapy of depression. Clin Psychol Sci Pract. 2022;29(3):294–303.
20. Cuijpers P, Karyotaki E, Weitz E, Andersson G, Hollon SD, van Straten A. The effects of psychotherapies for major depression in adults on remission, recovery and improvement: a meta-analysis. J Affect Disord. 2014;159:118–26.
21. De Carlo V, Calati R, Serretti A. Socio-demographic and clinical predictors of non-response/non-remission in treatment resistant depressed patients: a systematic review. Psychiatry Res. 2016;30(240):421–30.
22. Cuijpers P, Miguel C, Ciharova M, Harrer M, Basic D, Cristea IA, et al. Absolute and relative outcomes of psychotherapies for eight mental disorders: a systematic review and meta-analysis. World Psychiatry. 2024;23(2):267–75.
23. Wells JE, Browne MO, Aguilar-Gaxiola S, Al-Hamzawi A, Alonso J, Angermeyer MC, et al. Drop out from out-patient mental healthcare in the World Health Organization's World Mental Health Survey initiative. Br J Psychiatry. 2013;202(1):42–9.
24. Chisholm D, Sweeny K, Sheehan P, Rasmussen B, Smit F, Cuijpers P, et al. Scaling-up treatment of depression and anxiety: a global return on investment analysis. Lancet Psychiatry. 2016;3(5):415–24.
25. Cohen ZD, DeRubeis RJ. Treatment selection in depression. Annu Rev Clin Psychol. 2018;14(1):209–36.
26. Deisenhofer AK, Barkham M, Beierl ET, Schwartz B, Aafjes-van Doorn K, Beevers CG, et al. Implementing precision methods in personalizing psychological therapies: barriers and possible ways forward. Behav Res Ther. 2024;172:104443.
27. Nye A, Delgadillo J, Barkham M. Efficacy of personalized psychological interventions: a systematic review and meta-analysis. J Consult Clin Psychol. 2023;91(7):389–97.
28. Cuijpers P, Reynolds CF, Donker T, Li J, Andersson G, Beekman A. Personalized treatment of adult depression: medication, psychotherapy, or both? A systematic review. Depress Anxiety. 2012;29(10):855–64.
29. Kessler RC. The potential of predictive analytics to provide clinical decision support in depression treatment planning. Curr Opin Psychiatry. 2018;31(1):32–9.
30. Kessler RC, van Loo HM, Wardenaar KJ, Bossarte RM, Brenner LA, Cai T, et al. Testing a machine-learning algorithm to predict the persistence and severity of major depressive disorder from baseline self-reports. Mol Psychiatry. 2016;21(10):1366–71.
31. Lee Y, Ragguett RM, Mansur RB, Boutilier JJ, Rosenblat JD, Trevizol A, et al. Applications of machine learning algorithms to predict therapeutic outcomes in depression: a meta-analysis and systematic review. J Affect Disord. 2018;1(241):519–32.
32. Ermers NJ, Hagoort K, Scheepers FE. The predictive validity of machine learning models in the classification and treatment of major depressive disorder: state of the art and future directions. Front Psychiatry. 2020;11. Available from: https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2020.00472/full. Cited 2025 Feb 24.
33. Chekroud AM, Bondar J, Delgadillo J, Doherty G, Wasil A, Fokkema M, et al. The promise of machine learning in predicting treatment outcomes in psychiatry. World Psychiatry. 2021;20(2):154–70.
34. Puac-Polanco V, Ziobrowski HN, Ross EL, Liu H, Turner B, Cui R, et al. Development of a model to predict antidepressant treatment response for depression among Veterans. Psychol Med. 2023;53(11):5001–11.
35. VanderWeele TJ, Luedtke AR, van der Laan MJ, Kessler RC. Selecting optimal subgroups for treatment using many covariates. Epidemiology. 2019;30(3):334–41.
36. Luedtke A, Sadikova E, Kessler RC. Sample size requirements for multivariate models to predict between-patient differences in best treatments of major depressive disorder. Clin Psychol Sci. 2019;7(3):445–61.
37. Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam JD, Shelton RC, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA. 2010;303(1):47–53.
38. Driessen E, Cuijpers P, Hollon SD, Dekker JJM. Does pretreatment severity moderate the efficacy of psychological treatment of adult outpatient depression? A meta-analysis. J Consult Clin Psychol. 2010;78(5):668–80.
39. Phillips ML, Chase HW, Sheline YI, Etkin A, Almeida JRC, Deckersbach T, et al. Identifying predictors, moderators, and mediators of antidepressant response in major depressive disorder: neuroimaging approaches. Am J Psychiatry. 2015;172(2):124–38.
40. Fonseka TM, MacQueen GM, Kennedy SH. Neuroimaging biomarkers as predictors of treatment outcome in major depressive disorder. J Affect Disord. 2018;233:21–35.
41. Patel V, Weobong B, Weiss HA, Anand A, Bhat B, Katti B, et al. The Healthy Activity Program (HAP), a lay counsellor-delivered brief psychological

treatment for severe depression, in primary care in India: a randomised controlled trial. Lancet. 2017;389(10065):176–85.
42. Weobong B, Weiss HA, McDaid D, Singla DR, Hollon SD, Nadkarni A, et al. Sustained effectiveness and cost-effectiveness of the Healthy Activity Programme, a brief psychological treatment for depression delivered by lay counsellors in primary care: 12-month follow-up of a randomised controlled trial. PLoS Med. 2017;14(9):e1002385.
43. Veal C, Tomlinson A, Cipriani A, Bulteau S, Henry C, Müh C, et al. Heterogeneity of outcome measures in depression trials and the relevance of the content of outcome measures to patients: a systematic review. Lancet Psychiatry. 2024;11(4):285–94.
44. Chan AW, Boutron I, Hopewell S, Moher D, Schulz KF, Collins GS, et al. SPIRIT 2025 statement: updated guideline for protocols of randomised trials. Lancet. 2025;405(10491):e19-27.
45. India G of. Census 2011. 2011. Available from: https://censusindia.gov.in/.
46. Madhya Pradesh Population 2025. Available from: https://worldpopulationreview.com/regions/madhya-pradesh. Cited 2025 May 11.
47. Suryanarayana MH, Agrawal A, Prabhu KS. Inequality-adjusted human development index: states in India. Indian J Hum Dev. 2016;10(2):157–75.
48. Menon P, Deolalikar A, Bhaskar A. The India State Hunger Index: comparisons of hunger across States. 2008.
49. Shidhaye R, Lyngdoh T, Murhar V, Samudre S, Krafft T. Predictors, help-seeking behaviour and treatment coverage for depression in adults in Sehore district. India BJPsych Open. 2017;3(5):212–22.
50. Roberts T, Shidhaye R, Patel V, Rathod SD. Health care use and treatment-seeking for depression symptoms in rural India: an exploratory cross-sectional analysis. BMC Health Serv Res. 2020;20(1):287.
51. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–13.
52. Lee YC, Lee SC, Chiu EC. Practice effect and test-retest reliability of the mini-mental state examination-2 in people with dementia. BMC Geriatr. 2022;22(1):67.
53. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266–77.
54. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform. 2019Jul;1(95):103208.
55. Trials Unit (CHaRT) | Aberdeen Centre for Evaluation | The University of Aberdeen. Available from: https://www.abdn.ac.uk/ace/what-we-do/chart/. Cited 2025 Apr 15.
56. Berger VW, Ivanova A, Deloria KM. Minimizing predictability while retaining balance through the use of less restrictive randomization procedures. Stat Med. 2003;22(19):3017–28.
57. Zhao W, Berger VW, Yu Z. The asymptotic maximal procedure for subject randomization in clinical trials. Stat Methods Med Res. 2018;27(7):2142–53.
58. MHIN. Sangath & LSHTM (2013) Healthy activity program manual. Available from: https://www.mhinnovation.net/collaborations/toolkit-integration-mental-health-general-healthcare-humanitarian-settings/sangath. Cited 2025 Apr 13.
59. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018;391(10128):1357–66.
60. Ministry of Health and Family Welfare, Government of India. National list of essential medicines 2022. New Delhi: Government of India; 2022.
61. Patel V, Chisholm D, Rabe-Hesketh S, Dias-Saxena F, Andrew G, Mann A. Efficacy and cost-effectiveness of drug and psychological treatments for common mental disorders in general health care in Goa, India: a randomised, controlled trial. Lancet. 2003;361(9351):33–9.
62. Lalit V, Appaya PM, Hegde RP, Mital AK, Mittal S, Nagpal R, et al. Escitalopram versus citalopram and sertraline: a double-blind controlled, multicentric trial in Indian patients with unipolar major depression. Indian J Psychiatry. 2004;46(4):333.
63. Singla DR, Weobong B, Nadkarni A, Chowdhary N, Shinde S, Anand A, et al. Improving the scalability of psychological treatments in developing countries: an evaluation of peer-led therapy quality assessment in Goa. India Behav Res Ther. 2014;1(60):53–9.
64. Singla DR, Ratjen C, Krishna RN, Fuhr DC, Patel V. Peer supervision for assuring the quality of non-specialist provider delivered psychological intervention: lessons from a trial for perinatal depression in Goa, India. Behav Res Ther. 2020;1(130):103533.
65. Patel V, Weobong B, Nadkarni A, Weiss HA, Anand A, Naik S, et al. The effectiveness and cost-effectiveness of lay counsellor-delivered psychological treatments for harmful and dependent drinking and moderate to severe depression in primary care in India: PREMIUM study protocol for randomized controlled trials. Trials. 2014;15(1):101.
66. Fritz MS, MacKinnon DP. Required sample size to detect the mediated effect. Psychol Sci. 2007;18(3):233–9.
67. VanderWeele T. Explanation in causal inference: methods for mediation and interaction. New York: Oxford University Press; 2015.
68. Kenny DA, Judd CM. Power anomalies in testing mediation. Psychol Sci. 2014;25(2):334–9.
69. Center for Economic and Social Research. NubiS survey software system. Center for Economic and Social Research; 2025. Available from: https://github.com/nubissurveying/nubis.
70. Singla DR, Fernandes L, Savel K, Shah A, Agrawal R, Bhan A, et al. Scaling up the task-sharing of psychological therapies: a formative study of the PEERS smartphone application for supervision and quality assurance in rural India. Glob Ment Health (Camb). 2024;5(11):e20.
71. DeRubeis RJ, Cohen ZD, Forand NR, Fournier JC, Gelfand LA, Lorenzo-Luaces L. The personalized advantage index: translating research on prediction into individualized treatment recommendations. A demonstration. PLOS ONE. 2014;9(1):e83875.
72. van der Laan MJ, Polley EC, Hubbard AE. Super learner. Stat Appl Genet Mol Biol. 2007;6:Article25.
73. Luedtke AR, van der Laan MJ. Super-learning of an optimal dynamic treatment rule. Int J Biostat. 2016;12(1):305–32.
74. Zainal NH, Benjet C, Albor Y, Nuñez-Delgado M, Zambrano-Cruz R, Contreras-Ibáñez CC, et al. Statistical methods to adjust for the effects on intervention compliance in randomized clinical trials where precision treatment rules are being developed. Int J Methods Psychiatr Res. 2025;34(1):e70005.
75. Lu C, Tsai S, Ruhumuriza J, Umugiraneza G, Kandamutsa S, Salvatore PP, et al. Tracking rural health facility financial data in resource-limited settings: a case study from Rwanda. PLoS Med. 2014;11(12):e1001763.
76. The world health report. 2000: Health systems: improving performance. Geneva, Switzerland: World Health Organization; 2000.
77. Chisholm D, Knapp MRJ, Knudsen HC, Amaddeo F, Gaite L, van Wijngaarden B, et al. Client socio-demographic and service receipt inventory – European version: development of an instrument for international research: EPSILON study 5. Br J Psychiatry. 2000;177(S39):s28-33.
78. Moulton LH, Zeger SL. Analyzing repeated measures on generalized linear models via the bootstrap. Biometrics. 1989;45(2):381–94.
79. Efron B, Tibshirani RJ. An introduction to the bootstrap. New York: Chapman and Hall/CRC; 1994.
80. VanderWeele TJ, Vansteelandt S. Mediation analysis with multiple mediators. Epidemiol Methods. 2014;2(1):95–115.
81. Qiagen. QIAamp DNA blood mini handbook. Qiagen; 2020. Available from: https://www.qiagen.com/us/resources/resourcedetail?id=3f59e841-93c0-4d39-b5c1-c55ae524e3b6&lang=en.
82. Thermo Fisher Scientific. Qubit™ dsDNA HS assay kit user guide. Thermo Fisher Scientific; 2021. Available from: https://www.thermofisher.com.
83. Thermo Fisher Scientific. NanoDrop™ 2000/2000c spectrophotometer user manual. Thermo Fisher Scientific; 2012. Available from: https://assets.thermofisher.com.
84. Lucena-Aguilar G, Sánchez-López AM, Barberán-Aceituno C, Carrillo-Ávila JA, López-Guerrero JA, Aguilar-Quesada R. DNA source selection for downstream applications based on DNA quality indicators analysis. Biopreserv Biobank. 2016;14(4):264–70.
85. Illumina. Infinium global screening array-24 kit. Illumina; 2021. Available from: https://sapac.illumina.com/products/by-type/microarray-kits/infinium-global-screening.html.
86. Wray NR, Lin T, Austin J, McGrath JJ, Hickie IB, Murray GK, et al. From basic science to clinical application of polygenic risk scores: a primer. JAMA Psychiat. 2021;78(1):101–9.
87. Ge T, Chen CY, Ni Y, Feng YCA, Smoller JW. Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nat Commun. 2019;10(1):1776.

88. Ruan Y, Lin YF, Feng YCA, Chen CY, Lam M, Guo Z, et al. Improving polygenic prediction in ancestrally diverse populations. Nat Genet. 2022;54(5):573–80.
89. Thermo Fisher Scientific Inc. TaqMan® copy number assays and TaqMan® SNP genotyping assays: applied biosystems™\ Real-time PCR systems user guide. Thermo Fisher Scientific Inc.; 2020. Available from: https://www.thermofisher.com.
90. Siemens Healthcare Diagnostics Inc. CardioPhase® hsCRP Assay Instructions for Use – BN Systems [Internet]. Siemens Healthcare Diagnostics Inc.; 2020. Available from: https://www.siemens-healthineers.com.
91. Leuchter AF, Cook IA, Hunter AM, Korb AS. A new paradigm for the prediction of antidepressant treatment response. Dialogues Clin Neurosci. 2009;11(4):435–46.
92. Delgadillo J, Ali S, Fleck K, Agnew C, Southgate A, Parkhouse L, et al. Stratified care vs stepped care for depression. JAMA Psychiat. 2022;79(2):1–9.

Publisher's Note