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A Pilot Study of a Precision Treatment Trial Comparing Psychotherapy and Antidepressants for Depression in Indian Primary Care Settings

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Depression is commonly treated with either psychotherapy or antidepressants, but patients differ widely in their comparative responses. Identifying the most effective treatment for each individual is crucial to optimizing scarce resources, particularly in low-resource settings. This study evaluated the feasibility and acceptability of a precision treatment trial comparing psychotherapy based on behavioral activation (the Healthy Activity Program) with antidepressant medication (fluoxetine) in adults with depression in primary care settings in India. A single-blind, two-arm randomized controlled pilot was conducted with adults aged ≥18 years with moderate to severe depression (PHQ-9 score≥10) from eight primary healthcare centers in Bhopal, India. Primary outcomes were feasibility and acceptability, assessed using indicators of study implementation (recruitment, randomization, treatment fidelity, completeness of assessments, biologic sample collection, and safety) and participant engagement (retention and treatment adherence). Secondary outcomes included changes in depressive symptoms, remission, and patients' subjective sense of improvement at the 3-month endpoint. Of 578 individuals screened, 180 were eligible and 76 (42%) enrolled. Retention was 82% at 3 months. Psychotherapy participants attended 5.6/6-8 sessions, while medication participants consumed 57.9% of prescribed doses. Completion rates of study assessments were high (72–100%), and missing data were minimal, although some baseline measures were burdensome and were subsequently shortened for the main trial. Biologic sample collection was feasible, with 67% of participants consenting to blood draws. Depressive symptoms improved across both arms, with 45.2% achieving remission. However, treatment responses varied substantially within each arm (psychotherapy: –9.1 [SD = 6.5]; medication: –7.6 [SD = 6.9]), indicating marked individual heterogeneity. This pilot demonstrated the feasibility and acceptability of implementing a precision treatment trial for depression in Indian primary care, identified refinements to optimize procedures for the main trial, and supported the potential to identify the optimal treatment for each patient.

Keywords: depression; primary care; behavioral activation; antidepressants; precision mental health

Depression is one of the most common mental disorders and a leading cause of disability worldwide (Ferrari et al., 2024). Evidence-based treatments such as psychotherapy (including behavioral activation) and antidepressant medications are each comparably effective on average (Cuijpers et al., 2020). However, treatment response varies substantially, with some patients responding to only one or the other, to both, or to neither (Cuijpers et al., 2013; Kaiser et al., 2022; Maslej et al., 2021). As a result, many patients undergo a difficult, prolonged, costly, and inefficient trial-and-error process before finding a treatment that works for them.

Precision mental health aims to move beyond this "one-size-fits-all" approach by identifying patient-level characteristics that predict the most effective intervention for a given patient before treatment begins (Cohen & DeRubeis, 2018; DeRubeis, 2019). If such a strategy could be developed, it would offer the potential for earlier symptom relief, reduced burden on patients and providers, and more efficient use of healthcare resources. Previous research has shown promising results in developing algorithms that use clinical, demographic, and psychosocial characteristics to guide treatment selection for depression, helping identify the optimal treatment for a given patient from the outset (Chekroud et al., 2021; DeRubeis et al., 2014; Kappelmann et al., 2020; Kessler et al., 2017; LoParo et al., 2025; Lorenzo-Luaces et al., 2021).

Despite its promise, current precision mental health treatment research faces important limitations. Most studies have been conducted in small, homogeneous samples drawn from secondary psychiatric facilities in high-income countries, limiting their relevance to diverse, low-resource primary care settings (Chekroud et al., 2021; DeRubeis et al., 2014; Kappelmann et al., 2020; Kessler et al., 2017; LoParo et al., 2025; Lorenzo-Luaces et al., 2021; Luedtke et al., 2019). In addition, many precision treatment studies have included only a narrow range of patient characteristics (Kessler et al., 2017), focused on comparisons within the same treatment modality (Delgadillo et al., 2016; Puac-Polanco et al., 2023), or relied on expensive biomarkers, such as neuroimaging or genomic assays, which are not feasible to scale in routine primary care settings (Fonseka et al., 2018; Phillips et al., 2015).

Identifying the most effective treatment for a given patient is particularly critical in low-resource settings such as India, where primary healthcare facilities are often the first (and sometimes only) point of contact for mental health concerns (Patel et al., 2008). This early contact represents the best opportunity for the timely detection of illness and the prompt initiation of care. Yet depression remains highly prevalent among primary care attendees (affecting up to one-third of patients in some settings), and most cases go undetected and untreated (Fekadu et al., 2022). In India, an estimated 90% of the approximately 50 million individuals with depression receive no care (Sagar et al., 2020; Patel et al., 2016). This treatment gap delays recovery and strains already overstretched healthcare systems that must manage the physical conditions frequently co-occurring with or exacerbated by untreated depression (Chisholm et al., 2016; Rathod et al., 2017), highlighting the urgent need for practical and scalable approaches to optimize care.

To address these challenges, we designed the Optimizing Depression (OptimizeD) trial, a large-scale precision trial aimed at developing and validating a contextually grounded precision treatment model for depression in primary care in India (Pozuelo et al., 2025). Given the central role of primary care in the detection and management of depression, and the substantial unmet need in these settings, this context provides a critical opportunity to develop scalable treatment strategies in settings where optimizing limited healthcare resources is particularly important. The OptimizeD trial will randomize 1,500 patients with moderate to severe depression to receive either a culturally adapted psychotherapy based on behavioral activation (the Healthy Activity Program; HAP [Patel et al., 2017; Weobong et al., 2017]) or antidepressant medication (ADM, fluoxetine). Both treatments were designed for delivery by non-specialist providers and have been previously evaluated in Indian primary care settings (Patel et al., 2003, 2017; Weobong et al., 2017), supporting their feasibility for implementation in this context. This study presents results from the OptimizeD pilot phase, in which 76 adults were randomly assigned to receive HAP or ADM. Because the goal of the main trial is to develop a precision treatment rule, the current pilot was required to establish whether the methodological components required for such a trial could be successfully implemented in routine primary care. These included: (1) comprehensive multidomain baseline phenotyping of sufficient completeness and quality to support the development of a precision treatment rule (Pozuelo et al., 2026); (2) biological sample collection; (3) delivery of both interventions with sufficient fidelity and adherence to detect heterogeneity in treatment response; and (4) implementation of the operational infrastructure required for a large multisite trial. Accordingly, the pilot evaluated the feasibility and acceptability of these components through established implementation outcomes, including recruitment, randomization, treatment fidelity, retention, treatment adherence, data quality, biological sample collection, and safety procedures. These implementation domains were selected to identify operational barriers, evaluate whether they could be addressed through protocol refinements, and inform the design and implementation of the main trial. The primary objective was to assess the feasibility and acceptability of the study design and procedures, while secondary objectives examined changes in depressive symptoms, remission, and patients' subjective sense of improvement.

Methods

TRIAL DESIGN

The OptimizeD pilot study was a phase III, single-blind, two-arm, individual, parallel-group randomized controlled trial. Eligible participants were randomized to one of the two treatment arms (HAP or ADM) in an equal allocation ratio. There were six study assessments: baseline, mid-treatment (weeks 1, 2, 3, and 6), and posttreatment (3 months; primary endpoint). This study adhered to the Consolidated Standards of Reporting Trials (CONSORT) extension for pilot and feasibility trials (Table A1 in the Supplementary Materials) (Eldridge et al., 2016).

STUDY SETTING

The pilot study took place in the city of Bhopal, the capital of Madhya Pradesh, a centrally located Indian state with a population exceeding 87 million (Gov. of India, 2011; World Population, 2024). This state ranks among the poorest states of the country in terms of human development and has some of the highest national levels of food insecurity and undernutrition (Menon et al., 2008; Suryanarayana et al., 2016). The recruitment sites comprised eight public primary healthcare centers chosen according to predefined criteria, including: (1) presence of a Medical Officer authorized to prescribe antidepressants; (2) on-site pharmacist; (3) proximity to a laboratory for storing biological specimens; and (4) access to a private space for conducting assessments. Research in comparable settings suggests a point prevalence of moderate

to severe depression of approximately 17% (Roberts et al., 2020; Shidhaye et al., 2017).

PARTICIPANTS

Participants were eligible for inclusion if they met the following criteria: (1) provided informed consent, with adaptations made for illiterate participants to ensure understanding and compliance with local regulations; (2) aged 18 years or older; (3) attended one of the participating Primary Healthcare Centers; and (4) scored 10 or above on the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001). Exclusion criteria were as follows: (1) women who are pregnant, lactating or breastfeeding; (2) a history of psychosis or bipolar disorder; (3) plans to relocate outside Bhopal during the follow-up period; (4) cognitive impairment (assessed using the Mini-Mental State Examination-2; Lee et al., 2022); (5) inability to speak Hindi or English (the former being the primary language of the region); (6) patients undergoing treatment for depression at the time of recruitment; and (7) patients at imminent risk of suicide, determined by the Columbia Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011) and evaluation by the trial psychiatrist or psychologist. Participants with other nonpsychotic comorbidities were not excluded to reflect the heterogeneity typical of primary care populations. No exclusions were made based on race, caste, ethnicity, or religion. Participants' sociodemographic characteristics are shown in Table 1. The average age of participants was 37.7 years (SD 13.6), 62% were female, and most were married. Participants had an average of 10 years of education, and approximately half were employed across various occupations (most commonly laborers, domestic workers, or farmers). The majority were Hindu (74%), lived in urban areas (83%), and belonged to the General category (37%) or Other Backward Classes (36%).

STUDY MEASURES

Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a 9-item measure of depressive symptom frequency, with items rated on a 4-point Likert scale from 0 (*not at all*) to 3 (*nearly every day*). Total scores range from 0 to 27, with higher scores indicating greater symptom severity (Kroenke et al., 2001). The PHQ-9 has been validated for use in Indian populations, including in primary care settings (Avasthi et al., 2008; Ganguly et al., 2013; Patel et al., 2008), and the Hindi version used in this study has been validated against DSM-IV criteria in Indian patients (Kochhar et al., 2007). Scores of $\geq$10 and <5 were used to define moderate to severe depression and remission, respectively, consistent with established PHQ-9 thresholds (Kroenke et al., 2001; Manea et al., 2012; Rush et al., 2006) and prior studies in similar populations, including the original HAP trial (Ganguly et al., 2013; Indu et al., 2018; Patel et al., 2017; Weobong et al., 2017). All PHQ-9 administrations were conducted in Hindi. Research assistants read each item and its response options aloud to participants, who responded verbally; responses were then recorded by the research assistant on a tablet. This standardized procedure was used consistently across all participants, ensuring that literacy was not a barrier to completing the measure. Internal consistency of the PHQ-9 in the screened sample was $\alpha = 0.78$, indicating good and acceptable reliability (Tavakol & Dennick, 2011).

Quality of Behavioral Activation Scale (Q-BAS)

Therapy quality was assessed using the 20-item Q-BAS, rated on a 5-point Likert scale with higher scores reflecting better implementation quality (Singla et al., 2014). The scale assesses both treatment-specific skills (e.g., use of the behavioral activation model, activity scheduling, problem-solving) and general therapeutic competencies (e.g., rapport-building, empathy, collaboration). The Q-BAS was adapted from earlier behavioral activation fidelity measures (Dimidjian et al., 2012) to capture components specific to HAP, and has since been adapted for use in related interventions (Singla, Ratjen, et al., 2020; Singla et al., 2023). It has been successfully used to assess therapy quality to behavioral activation in lay counselor-delivered interventions in low-resource primary care settings in India, demonstrating good internal consistency, excellent inter-rater reliability, and predictive validity in varied settings and treatment providers (Singla et al., 2014, 2023; Singla, Hollon, et al., 2020). As part of routine supervision, audio-recorded sessions were rated by counselors, peers, and supervisors to support ongoing quality monitoring and feedback. HAP treatment fidelity was assessed by an independent expert who was not affiliated with the study team but was involved in the original development and delivery of HAP, and who had extensive experience rating HAP sessions across multiple trials in India. The independent expert used the Q-BAS to rate a random sample of sessions stratified by counselor and treatment phase, with a prespecified minimum target of 10% of sessions, following the approach used in the original HAP trial (Patel et al., 2017). In the current study, the Q-BAS demonstrated good to excellent internal

Table 1
Sociodemographic Characteristics

	Total (N = 76)	ADM (N = 38)	HAP (N = 38)	p-value
Age	37.7 (13.6)	37.9 (14.4)	37.5 (13.0)	0.91
Male	38.2%	36.8%	39.5%	0.81
Marital status				0.90
Single	25%	24%	26%	
Married or living together	59%	58%	61%	
Divorced, Separated	5%	5%	5%	
Widowed	11%	13%	8%	
Enrolled in school	13.2%	10.5%	15.8%	0.50
Years of education	9.8 (4.0)	9.2 (4.1)	10.4 (3.8)	0.22
Full or part-time employed	45.9%	43.2%	48.6%	0.64
Occupation				0.56
Student	9%	8%	11%	
Unemployed	16%	18%	13%	
Housewife	18%	16%	21%	
Laborer, domestic worker, farmer	22%	29%	16%	
Trader, food seller	5%	8%	3%	
Seamstress, hairdresser	5%	3%	8%	
Clerical, secretarial, peon	7%	5%	8%	
Professional (teacher, nurse, accounts, administrative)	16%	11%	21%	
Missing	1%	3%	0%	
Caste				0.26
Other Backward Classes	36%	26%	45%	
Scheduled caste	22%	29%	16%	
Scheduled tribe	3%	3%	3%	
General	37%	37%	37%	
Missing	3%	5%	0%	
Religion				0.27
Hinduism	74%	79%	68%	
Islam	25%	18%	32%	
Christian	1%	3%	0%	
Setting				0.53
Urban	83%	79%	87%	
Suburban	1%	3%	0%	
Rural	14%	16%	13%	
Other	1%	3%	0%	
Household asset index (0 – 100)	61.5 (17.5)	60.9 (18.7)	62.1 (16.4)	0.77
PHQ9 score at screening	15.0 (3.6)	15.0 (3.7)	15.0 (3.5)	1.00
Severity				0.95
Moderate	45%	45%	45%	
Moderately severe	38%	39%	37%	
Severe	17%	16%	18%	

Note. ADM = antidepressant medication (fluoxetine); HAP = Healthy Activity Program.

consistency across counselors, supervisors, and fidelity assessors ($\alpha = 0.84–0.93$).

Patients' Subjective Improvement

This was assessed using two single-item global rating questions on perceived changes in overall health and tension over the 3 months since study entry. Responses were recorded on a 4-point scale ranging from "became worse" to "fully recovered." These items were taken directly from the original HAP trial (Patel et al., 2017; Weobong et al., 2017).

STUDY PROCEDURES

The consent process was conducted by trained and supervised research assistants, who approached individuals attending primary healthcare clinics. Participants who met the eligibility criteria received detailed information about the study, including its objectives, procedures, and risks, before providing informed consent. To evaluate the consent process, assessors were trained and periodically supervised using audio-recordings of the consent sessions (recorded only when participants provided permission to do so) to confirm

that all study elements were clearly explained and understood. Consent audio-recordings were reviewed primarily by a supervising research coordinator, and on occasion by the trial manager, neither of whom was involved in the consent process. Reviews were conducted using a structured checklist that examined: (1) the accuracy of information conveyed (e.g., study objectives, procedures, time commitment, confidentiality, and voluntary participation); and (2) the clarity of explanation, response to participant questions, and communication quality (e.g., tone, absence of coercive language). Findings from these reviews served a dual purpose: they informed overall assessments of consent quality and were used to identify research assistants who required targeted refresher training to improve recruitment consistency across sites.

Those who met all eligibility criteria and provided consent completed a baseline assessment covering 68 constructs across multiple domains of interest, including clinical (e.g., depression severity, comorbidities), psychological (e.g., neuroticism, self-esteem), cognitive (e.g., shifting, inhibition), socioeconomic (e.g., poverty status, social support), and biological (e.g., inflammatory markers like C-reactive protein [CRP]) (see Table A2 for a complete list). The selection of constructs was informed by a systematic literature review to identify prognostic and prescriptive indices in the depression treatment literature, followed by refinement through an expert survey. The baseline development process is described elsewhere (Pozuelo et al., 2026).

As part of the baseline assessment, participants were invited to provide a blood sample to measure CRP levels and extract DNA for genome-wide single-nucleotide polymorphism (SNP) array genotyping. Blood collection was optional and not required for inclusion in the study, and was conducted as part of an exploratory aim to assess the added value of incorporating these biomarkers into the precision treatment rule developed in the larger trial. Initially, 10 mL of blood was drawn, but midway through the pilot, this volume was reduced to 5 mL after low consent rates indicated participant discomfort with the larger sample volume. Subsequent laboratory testing confirmed that DNA extracted from 3 mL of blood consistently met quality and concentration thresholds for genome-wide genotyping, and the remaining 2 mL was sufficient for CRP estimation. This adjustment substantially improved participant consent rates while maintaining sample adequacy for all planned analyses. CRP concentrations were measured using the Siemens BN ProSpec System with the CardioPhase hsCRP Kit (Siemens Healthcare Diagnostics Inc., 2020), following the manufacturer's protocol. DNA extraction methods were tested to identify a feasible protocol yielding high-quality DNA. An initial centrifugation-based method produced low DNA concentrations (Qiagen, 2020), leading to the adoption of a gravity-sedimentation protocol that generated markedly higher yield and purity. Genome-wide genotyping (GSA) was performed using the Illumina Global Screening Array (Illumina, Inc., 2025) with standard quality-control procedures, and supplementary CYP2D6 assays were conducted using TaqMan methods (Applied Biosystems, 2016; Thermo Fisher Scientific Inc., 2020). Detailed laboratory protocols, yield and purity metrics, and genotyping quality-control procedures are provided in the Supplementary Materials.

On completion of the baseline assessment, participants were randomized to one of the two treatment arms (described below). Subsequent study visits occurred at weeks 1, 2, 3, and 6, with the primary endpoint at 3 months. The PHQ-9 was administered at all time points. Participants who endorsed the 9th item on suicidality were further assessed with the C-SSRS, and those identified as high risk were referred to the trial psychologist or psychiatrist for further evaluation. Baseline, week 3, week 6, and week 12 assessments also included potential mediators to be piloted for the larger trial (anhedonia, patient activation, social support, rumination, and emotion regulation). At baseline and week 12, we also administered a patient-level cost tool (Chisholm et al., 2000) for use in the larger trial's cost-effectiveness analysis. The week 12 assessment largely repeated the baseline battery (excluding demographics and prognostic constructs) and included two questions to assess patients' subjective improvement (Weobong et al., 2017). The assessment schedule is detailed in Table 2. All study assessments, except for the eligibility survey and baseline assessment, were conducted by trained outcome assessors.

RANDOMIZATION AND BLINDING

Participants were randomized using a computerized algorithm developed by CHaRT (Centre for Healthcare Randomised Trials) at the University of Aberdeen, an organization independent of the study team (Trials Unit (CHaRT) | Aberdeen Centre for Evaluation | The University of Aberdeen, n.d.). The algorithm used maximum tolerated imbalance procedures (Berger et al., 2003; Zhao et al., 2018) with a sliding window approach and three stratification factors: clinic, sex, and PHQ-9 score at intake

Table 2
Schedule of Assessments

Assessment	Screen	Baseline	Allocation	Acute treatment				
TIME POINT (W: weeks; M: months)	-t_2	-t_1	0	W1	W2	W3	W6	3M
Location	Clinic	Clinic	Clinic	Clinic /home/ phone	Clinic /home/ phone	Clinic /home/ phone	Clinic /home/ phone	Clinic / home
SCREENING								
Eligibility screen	X							
Informed consent	X							
Allocation			X					
INTERVENTION & PROCESS INDICATORS								
HAP treatment [n=38] *Process indicators*: HAP session information (sessions completed, homework completed); Therapist outcomes (supervision quality, counselors quality ratings, fidelity assessor's rating, etc.)			●	—	—	—	—	●
ADM treatment [n=38] *Process indicators:* Pill counts, appointment attendance, side effects, Adverse Reactions			●	—	—	—	—	●
ASSESSMENTS								
Depressive symptoms (PHQ9) *[Primary outcome]*	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), Social Support (MSPSS), Rumination (ARQ), Emotion Regulation (ERQ)		X				X	X	X
Post-intervention assessment: same as baseline (except demographic questionnaire and prognostic constructs) and patient-rated change.								X

Note. ADM = Antidepressant Medication, ARQ = Analytical Rumination Questionnaire, ERQ = Emotion Regulation Questionnaire; HAP = Healthy Activity Program, M = Months, MSPSS = Multidimensional Scale of Perceived Social Support; PAAS = Patient Activation Abbreviated Scale, PHQ-9 = Patient Health Questionnaire-9, SHAPS = Snaith-Hamilton Pleasure Scale, W = Weeks.

(<15 vs. ≥15). Participants were allocated using CHaRT's online software, and the trial manager oversaw the enrollment of participants. Outcome assessors responsible for follow-up assessments were blinded to participants' treatment allocation. If an outcome assessor was inadvertently unblinded, the participant was reassigned to a different blinded assessor, and the incident was documented. Given the distinct nature of the interventions, neither participants nor providers (counselors and medical officers) were blinded.

SAMPLE SIZE

As a pilot study, the sample size was determined to assess feasibility and acceptability rather than to test efficacy, and as such, no formal sample size calculation was performed. We enrolled 76 participants (approximately 10 per clinic), which we considered sufficient to test the feasibility of study procedures, address logistical challenges, and pilot study instruments for the larger OptimizeD trial. The pilot was not powered to detect between-arm differences in secondary outcomes.

INTERVENTIONS

Healthy Activity Program (HAP)

HAP is a brief, culturally adapted, manualized psychological treatment based on behavioral activation, an empirically supported approach recommended by the WHO that helps individuals reengage in rewarding, pleasurable, and meaningful activities (WHO, 2010). In the original trial evaluating HAP, 64% of participants with moderately severe to severe depression achieved at least partial remission (PHQ-9 score of <10) at 3 months, with sustained benefits observed at 12 months (Patel et al., 2017; Weobong et al., 2017). HAP involves 6–8 individual sessions, delivered weekly over a period of 3 months. Sessions last 30–40 minutes and are conducted face-to-face at the patient's home or another convenient location of their choice (or by phone if in-person is not feasible). HAP was originally designed for delivery by non-specialist providers. In this study, it was delivered by trained project counselors with undergraduate or graduate degrees in psychology, social work, or other related fields, but without prior counseling experience. HAP counselors receive 2 hours of weekly group supervision by experienced HAP supervisors and monthly one-on-one sessions by a clinical expert, focusing on case review, skill practice, and problem-solving. A detailed description of counselor selection, training, and supervision is described elsewhere (Patel et al., 2017; Weobong et al., 2017), and further details on the structure and content of HAP are available in the treatment manual (Sangath & LSHTM [2013] Healthy Activity Program Manual, n.d.).

Antidepressant Medication (ADM)

Participants randomized to the ADM arm received fluoxetine, a selective serotonin reuptake inhibitor (SSRI) widely supported by strong evidence for its safety and efficacy in depression treatment (Cipriani et al., 2018). Fluoxetine is part of India's Essential Medicines List (Ministry of Health and Family Welfare, Government of India, 2022) and is usually available for free in government health facilities. It has demonstrated effectiveness in primary care, as shown in a placebo-controlled trial in health-care settings in India that reported a 70% remission rate at 2 months (Patel et al., 2003), significantly higher than typical rates seen in meta-analyses (Cipriani et al., 2018). The acute treatment phase lasted 3 months, with follow-up visits at weeks 3, 6, and 12 to review tolerability and adjust the dose. Fluoxetine was initiated at 20 mg daily and could be increased to 40 mg depending on symptoms and side effects, or reduced to 10 mg if adverse effects occurred. After 3 months, participants entered a continuation phase (months 4–12) in which the dose was maintained or gradually tapered, giving a total planned treatment duration of 12 months. Escitalopram, also on India's Essential Medicines List (Ministry of Health and Family Welfare, Government of India, 2022), was offered as an alternative for participants unable to tolerate fluoxetine. Switching occurred at week 6, starting at 10 mg daily with an option to increase to 20 mg based on tolerance and response. These participants had an additional review at week 9 to monitor progress. All prescribing and follow-up sessions were conducted by medical officers based at the participating clinics. Any participant experiencing a serious adverse effect from fluoxetine or escitalopram was referred to specialist psychiatry care at the tertiary institution, All India Institute of Medical Sciences (AIIMS) in Bhopal.

OUTCOMES

The primary outcomes were feasibility and acceptability, selected in accordance with established frameworks for pilot and feasibility research (Craig et al., 2008; Eldridge et al., 2016; Lancaster et al., 2004). Feasibility was defined as the extent to which study procedures could be successfully implemented as planned within the target setting. Acceptability was defined as participants' willingness to engage with the assigned intervention and study procedures. Although related, these constructs are operationally distinct: feasibility reflects what could be done, while acceptability reflects what participants were willing to do. Both were operationalized using behaviorally anchored indicators commonly employed in pilot trials.

Feasibility was assessed through the following indicators: (1) *Recruitment procedures*: Enrollment rate among eligible participants, time required to recruit the target sample size and from screening to treatment initiation, and the feasibility of implementing a high-quality consent process; (2) *Randomization:* Successful allocation using the CHaRT online platform to evaluate whether the platform could be reliably implemented across distributed sites, including checks to ensure concealment and balance across stratification factors; (3) *Treatment fidelity*: HAP treatment fidelity was assessed using the Q-BAS by an independent expert (see Measures). For ADM, external fidelity ratings were not used, as these methods are less applicable to pharmacological care; instead, quality assurance focused on safe and effective medication delivery in line with the study protocol; (4) *Completeness and quality of study assessments:* Proportion of participants completing the baseline

and mid-treatment assessments (weeks 1, 2, 3, 6), data quality for all measures (e.g., item nonresponse, time-to-complete, and internal consistency), and the feasibility of biologic sample collection, including consent rates for blood draws, reasons for refusal, and the quality and completeness of biological specimens; and (5) *Safety and risk management*: Implementation of risk-monitoring procedures, including the use of the C-SSRS for suicide risk and established escalation pathways.

Acceptability was assessed through the following indicators of participants' engagement with the study and interventions: (1) *Retention in the study:* Proportion of participants who completed the 3-month primary endpoint; (2) *Treatment adherence:* Adherence in the HAP arm was determined by the number of therapy sessions attended, whereas in the ADM arm, it was measured as the percentage of the prescribed dose consumed, calculated using pill counts;

Secondary outcomes included: (1) *Changes in depressive symptoms* from baseline to 3 months, measured using the PHQ-9; (2) *Remission*, defined as a PHQ-9 score of <5; (3) *Patients' subjective improvement* (described in Measures).

STATISTICAL ANALYSIS

We summarized feasibility outcomes using descriptive statistics (proportions, means, SDs) for the total sample and by treatment arm. Secondary outcomes were analyzed on an intention-to-treat basis. Between-arm differences in PHQ-9 change scores were estimated with linear regression models adjusted for clinic and baseline PHQ-9 score, using robust standard errors. Results are presented as adjusted mean differences (AMDs) with 95% CIs. Remission rates were compared using logistic regression with the same covariate adjustments. A two-sided $p < 0.05$ was considered statistically significant. The analysis was conducted using Stata Version 17.0 (StataCorp, 2021).

Results

PRIMARY OUTCOMES

Feasibility

(1) Recruitment procedures. Participants were enrolled between August 17 and December 4, 2023 (Figure 1). The pilot trial concluded on February 27, 2024, with the completion of the 3-month endpoint assessment for the last participant enrolled. A total of 578 patients completed the eligibility screening survey. Of these, 398 (69%) were excluded for not meeting inclusion criteria, with 92% scoring below the PHQ-9 cutoff of 10. Among the 180 eligible participants, 104 declined to participate, most commonly (63%) citing lack of time as the main reason. The remaining 76 participants (42% of those eligible) provided informed consent and were enrolled in the study. Baseline characteristics did not differ between those who enrolled and eligible individuals who declined participation (Table A3). Reviews of consent audio-recordings indicated that research assistants generally conveyed study information with accuracy and empathy. The reviews pinpointed areas requiring clarification, particularly regarding time commitment and treatment plan adherence, and identified research assistants who needed targeted refresher training to ensure consistency across sites.

(2) Randomization. Randomization through the CHaRT online platform functioned reliably across sites. Baseline characteristics did not differ significantly between the treatment arms (Table 1), confirming successful allocation concealment and balance across stratification factors (clinic, sex, and PHQ-9 score at intake)

(3) Treatment fidelity. Independent fidelity ratings were completed for 17% of audio-recorded sessions, exceeding the prespecified minimum target of 10%. The additional rated sessions were used to provide targeted feedback and inform counselor training ahead of the main trial. Among the rated sessions, the average Q-BAS score (range: 0–4) was 2.6 (95% CI: 2.5, 2.8), indicating adequate but improvable fidelity to the behavioral activation treatment protocol. For antidepressant management, quality assurance focused on adherence to prescription protocols and safety monitoring rather than external fidelity ratings.

(4) Completeness and quality of study assessments. The baseline assessment battery required, on average, 217 minutes (SD = 92; median = 208) to complete. This length was burdensome for both participants and interviewers and was a key reason the battery was substantially shortened for use in the larger trial. Despite its length, missing data rates were low (<2% on average), and most multi-item scales demonstrated acceptable internal consistency (Figure A2). A post-fieldwork survey completed by interviewers and reviews of audio-recordings helped us identify problematic questions, which were modified for the larger trial, with implementation supported by additional training and the use of visual guides. All modifications to the baseline battery are documented in detail elsewhere (Pozuelo et al., 2026). Completion rates for the scheduled mid-treatment assessments (weeks 1, 2, 3, 6) averaged 78% across all participants (range: 72%–100%) and were not

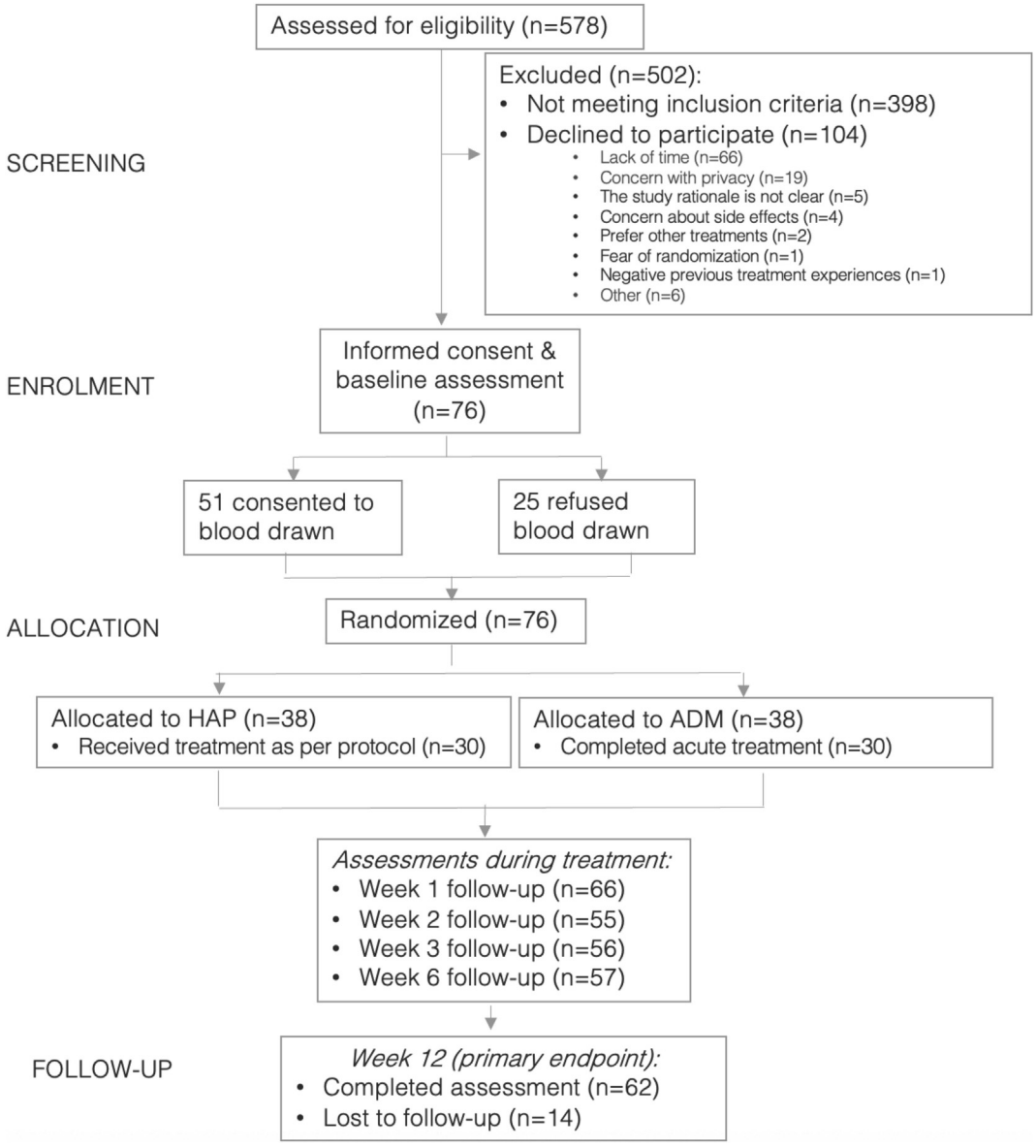

FIGURE 1 Study flow diagram. *Note*. ADM = antidepressant medication (fluoxetine); HAP = Healthy Activity Program.

statistically different between the two treatment arms at any follow-up point (p-value range: 0.17-0.44; Table A5). Although mid-treatment assessments were brief (about 6 minutes each), they were logistically challenging to implement, with participants requiring an average of two reminder calls per assessment. Barriers included switched-off phones, postponed assessments, and missed appointments. Further reflections on these logistical challenges and corresponding protocol refinements are presented in the Discussion.

Feasibility of Biologic Collection

Of the $N = 76$ participants enrolled, 51/76 (67%) consented to provide a blood sample at baseline, with no significant difference between treatment arms ($p = 0.23$). The most common reasons for refusal were fear of needles (52%) and apprehension about blood draws (20%). The low consent rate led the team to reduce the required blood volume from 10 to 5 mL, which helped re-engage eight participants who had initially refused. We also considered saliva sampling as a non-invasive alternative, and while this was not implemented in the pilot, it was incorporated into the larger trial. Of the participants who provided blood samples at baseline, 37.3% (19/51) had elevated CRP levels (>3.2 mg/L), indicating systemic inflammation in a substantial proportion of the sample. DNA quality differed by extraction protocol: the centrifugation method ($n = 19$) yielded low concentrations (mean = 5.15 ng/μL, SD = 3.94) and

poor purity (mean A260/280 = 0.99, SD = 0.17), whereas the modified gravity-sedimentation method (n = 32) produced markedly higher yields (mean = 78.30 ng/μL, SD = 46.87) and better purity (mean A260/280 = 1.80, SD = 0.05), resulting in intact, high-quality DNA suitable for downstream analysis. Genome-wide genotyping was successfully performed on 32 samples, with all data passing initial quality control checks.

(5) Safety and risk management. Implementation of risk-monitoring procedures was feasible across clinics. The C-SSRS was successfully administered at all time points, and escalation protocols were followed when participants reported suicidal ideation. No serious adverse events related to study procedures occurred during the pilot.

Acceptability

(1) Retention in the study. Figure 1 shows moderately high retention rates, with 82% (62/76) of enrolled participants completing the primary endpoint at 3 months. Retention did not differ significantly between treatment arms (p = 0.24) or across clinics (p = 0.61). Baseline characteristics were comparable between participants who completed follow-up and those lost to follow-up, with no statistically significant differences observed (Table A4).

(2) Treatment adherence. Treatment adherence was assessed using different metrics in each arm and is therefore not directly comparable (Table 3). Participants in the HAP arm attended an average of 5.6 therapy sessions (95% CI: 4.9, 6.4), with 30 participants (79%) receiving a planned discharge after completing treatment. Two participants did not attend any HAP sessions after enrollment. In the ADM arm, 30 participants completed the acute treatment phase according to the study protocol, which required taking the medication and attending scheduled visits with the medical officer. Two participants (aged 19 and 21 years) did not initiate antidepressant treatment because the medical officer was reluctant to prescribe medication, given their age, and one additional participant did not attend follow-up visits or take any medication. Across all participants allocated to the ADM group, including those who dropped out or did not initiate treatment, dose adherence was relatively low, with an average of 57.9% of prescribed medication consumed (95% CI: 47.0–68.9). One participant was switched to escitalopram due to tolerance issues. No adverse reactions requiring referral were reported, suggesting that side effects were unlikely to have contributed to low adherence.

Based on the feasibility findings reported above, the study team identified a set of protocol modifications to be implemented in the main OptimizeD trial. These are summarized in Table 4 and reflect challenges identified across all feasibility domains, with solutions developed through structured review meetings involving the full study team (including field research assistants, supervisors, the trial manager, and senior investigators). The proposed modifications were subsequently reviewed and approved by the Trial Steering Committee prior to implementation in the main trial.

SECONDARY OUTCOMES: DEPRESSIVE SYMPTOMS, REMISSION, AND PATIENTS' SUBJECTIVE SENSE OF IMPROVEMENT

Depressive symptoms improved significantly across both arms, with a mean PHQ-9 reduction from 15.0 (95% CI: 14.1–16.0) at baseline to 6.7 (95% CI: 5.2–8.2) at the 3-month primary endpoint (Figure 2). The comparative efficacy of the interventions in reducing symptoms of depression and achieving remission is shown in Table 5. Overall, 45.2% achieved remission (PHQ-9 < 5), with no significant differences in the PHQ-9 score or remission rates between interventions. Mean

Table 3
Treatment Adherence

HAP: Treatment Adherence	
Treatment status	**Average sessions received [95% CI]**
Total Patients allocated to HAP (n = 38)	5.6 [4.9, 6.4]
Planned discharge (n = 30)	6.7 [6.4, 7.0]
Unplanned discharge (n = 8)	1.5 [0.2, 2.8]
ADM: Treatment Adherence	
Treatment status	**Dose adherence [95% CI]**
Total Patients allocated to ADM (n = 38)	57.9% [47.0, 68.9]
Completed acute treatment (n = 30)	70.4% [61.3, 79.5]
Dropped out (n = 8)	11.3% [-2.7, 25.3]

Note. ADM = antidepressant medication (fluoxetine); HAP = Healthy Activity Program.

Table 4
Lessons Learned from Pilot Study: Challenges Encountered and Modifications for the Main Trial

Domain	Challenge Identified in Pilot	Solution Implemented for Main Trial
Recruitment	• 42% enrollment among eligible participants, with lack of time cited as the main barrier. • Recruitment took approximately 3.5 months to reach the target sample size. • Some clinics had very low enrollment, and delays occurred between screening and treatment initiation.	• Hired additional research assistants • Expanded number of clinical sites • Extended screening to weekends • Adjusted schedules around major festivals • Involved family members in screening process (especially for younger adults) • Concentrated recruitment in primary healthcare centers with higher patient volume
Informed Consent	• Audio-recording reviews identified unclear communication about time commitment and adherence expectations. • The consent process was lengthy and sometimes perceived as intimidating by participants.	• Developed a short study video to explain procedures more clearly • Strengthened staff capacity through peer buddy system • Enhanced training on communicating time commitment and treatment expectations • Created more supportive, less intimidating consent process • Provided targeted refresher training for specific research assistants to ensure cross-site consistency
Randomization	• Randomization through the CHaRT online platform functioned reliably across sites. • Occasional connectivity issues prevented online randomization.	• Retained CHaRT as main platform • Kept manual backup for rare connectivity failures
Retention	• 18% lost to follow-up at 3 months • Frequent contact from multiple team members caused fatigue and frustration	• Introduced flexible scheduling, including evenings, weekends, phone-based assessments • Improved rapport-building between participants and assessors • Improved coordination among team members to minimize extra reminder calls • Developed assessment reminder card for participants • Reduced number of study assessments from 6 to 4
Treatment Adherence	• HAP: Two participants did not start treatment • ADM: Low dose adherence and occasional reluctance to prescribe to younger participants.	• Introduced an abbreviated initial HAP session to strengthen counselor–participant rapport and prevent early disengagement • Increased medical officer training • Authorized trial psychiatrist to prescribe via telemedicine • Refined recruitment to set clearer expectations about continuing treatment even when feeling better • Introduced evening, weekend, and phone sessions for flexibility • Simplified documentation with single patient card

Treatment Fidelity	• Average Q-BAS score indicated adequate fidelity but with variation across counselors	• Provided more targeted counselor training • Placed greater emphasis on using fidelity reviews to guide supervision and problem-solving at the counselor level
Study assessments	• Baseline battery excessively long (mean 217 minutes) • Mid-treatment assessments (n = 6) logistically challenging (average of 2 reminder calls per participant/assessment) • Some measures difficult to administer • Quality concerns identified through audio-recording review	• Substantially shortened baseline battery • Reduced mid-treatment assessments from 6 to 4 • Introduced phone-based assessment option • Modified or removed problematic questions, and introduced visual guides • Introduced regular assessor training • Implemented systematic review of audio-recordings • Established periodic on-site checks
Biological Sample Collection	• Moderate consent rate for blood draws (67%), with fear of needles the main reason • Poor DNA quality with initial extraction protocol	• Reduced required blood volume from 10 mL to 5 mL • Adopted modified gravity-sedimentation extraction method • Added saliva sampling as alternative
Safety and Risk Management	• Risk-monitoring procedures were feasible, and escalation protocols worked effectively	• Standardized risk documentation and reporting forms • Added regular refresher training on suicide risk assessment and escalation procedures

Note. ADM = antidepressant medication (fluoxetine); CHaRT = Centre for Healthcare Randomised Trials; Q-BAS = Quality of Behavioral Activation Scale; HAP = Healthy Activity Program.

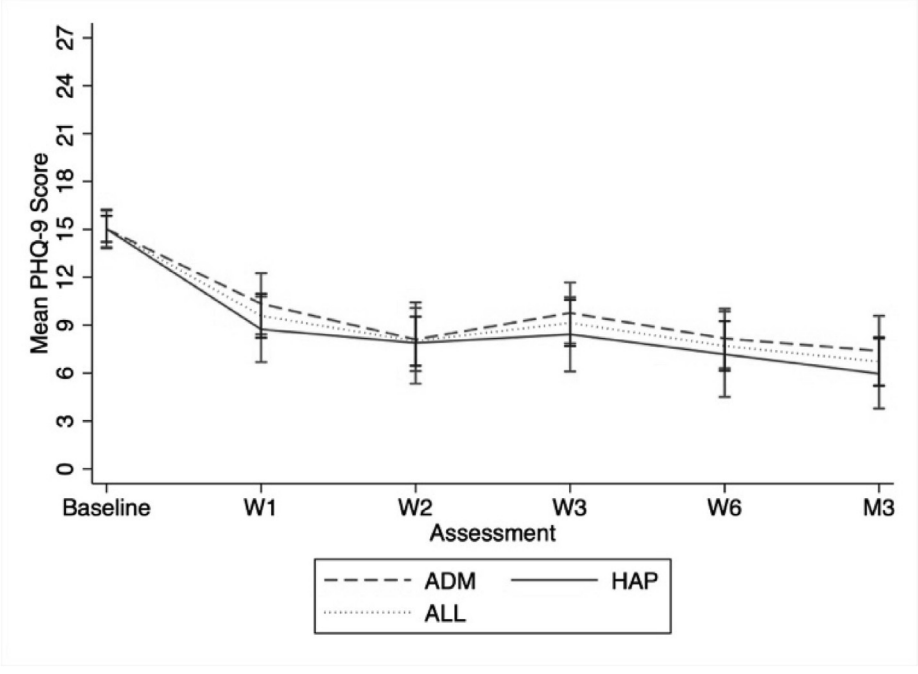

FIGURE 2 PHQ-9 scores over time by treatment arm. *Note*. ADM = antidepressant medication (fluoxetine); HAP = Healthy Activity Program.

change scores further illustrated the variability in response, with an average reduction of –9.1 (SD = 6.5) in the psychotherapy arm and –7.6 (SD = 6.9) in the antidepressant arm. This heterogeneity in improvement (range: –20 to +8) reflects considerable individual differences in treatment

Table 5
Depressive Symptom Severity, Change, and Remission Status at 3-Month Follow-up by Treatment Arm

	Total (N = 62)	ADM (N = 33)	HAP (N = 29)	Effect estimate[a] (95% CI)	p-value
Mean PHQ9 score at 3-months (SD)	6.7 (6.0)	7.4 (6.2)	6.0 (5.7)	-1.4 (-4.5, 1.7)	0.369
Mean change in PHQ-9 from baseline (SD)	-8.3 (6.7)	-7.6 (6.9)	-9.1 (6.5)	-1.4 (-4.8, 2.0)	0.403
ion: PHQ9 < 5 at 3-months, no. (%)	28 (45.2%)	16 (48.5%)	12 (41.4%)	OR = 0.7 (0.3, 2.1)	0.560

Note. ADM = antidepressant medication (fluoxetine); HAP = Healthy Activity Program; PHQ-9 = Patient Health Questionnaire-9; SD = standard deviation.

[a] Effect estimates compare HAP with ADM (HAP − ADM). The 3-month PHQ-9 mean difference and remission odds ratio were estimated using linear and logistic regression, respectively, adjusted for clinic and baseline PHQ-9 score, with robust standard errors. The PHQ-9 change-score difference was estimated using an unadjusted two-sample t-test.

response. As shown in Figure A1, outcomes in the antidepressant arm were more dispersed and bimodal, with some participants achieving remission while others showed minimal change. The HAP group had a slightly lower mean score overall, but outcomes were more tightly clustered and modestly right-skewed, indicating more consistent improvement but fewer participants crossing the remission threshold.

Subjective perceptions of improvement were also favorable. At the 3-month endpoint, the majority of participants (87.1%) reported that their overall health had improved, with 16.1% indicating they felt "fully recovered." Similarly, 81% of participants (50/62) reported improvements in tension, with 14.5% reporting being "fully recovered" (Figure 3). Comparisons between arms did not reveal statistically significant differences in these subjective ratings.

Discussion

This pilot trial demonstrated the feasibility and acceptability of conducting a precision trial delivering psychotherapy based on behavioral activation (HAP) and antidepressant medication (fluoxetine) for moderate to severe depression in Indian primary care settings. While retention was high and study procedures generally functioned as intended, recruitment was challenging and resulted in the identification of several operational barriers—each of which directly informed protocol refinements for the main trial (Table 4).

Enrollment among eligible participants was 42%, with lack of time cited as the most common reason for refusal. While this reflects the real-world demands placed on participants by a study requiring lengthy assessments and multiple follow-up visits, it also highlights the need for more flexible and proactive recruitment strategies.

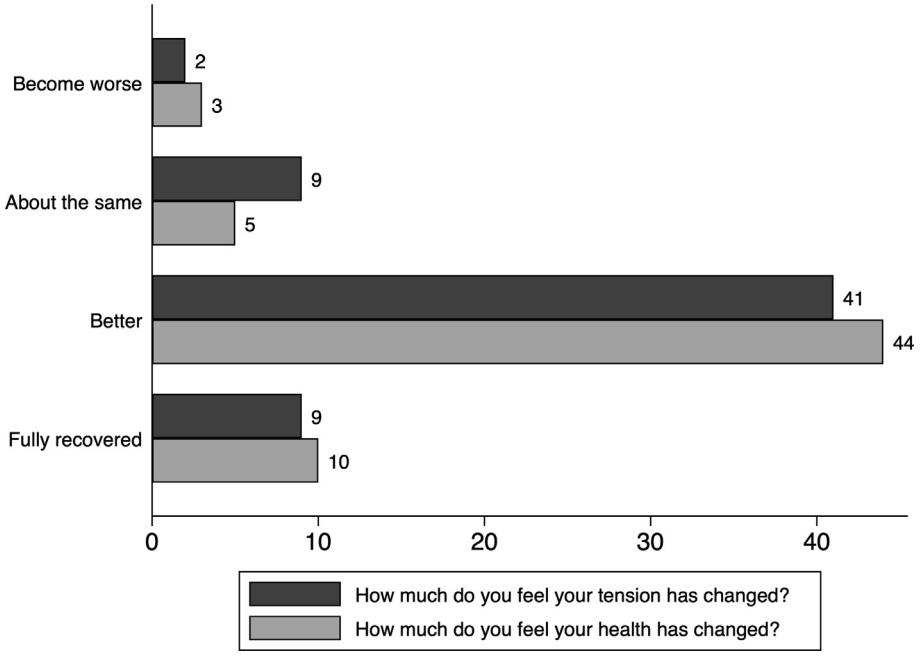

FIGURE 3 Patient's subjective improvement (n = 62). *Note*. One participant responded "Prefer not to say" to the tension question.

In response, recruitment was supported by hiring additional research assistants, expanding the number of sites, extending screening to weekends, and adjusting schedules around major festivals. Other refinements included involving family members in the screening process (particularly for younger participants), concentrating recruitment in clinics with higher numbers of eligible patients, strengthening staff capacity through a peer buddy system to support newer team members, and creating a more supportive and less intimidating consent process (e.g., by using a study video to explain procedures clearly). Retention was improved through flexible scheduling (including evening, weekend, and phone-based assessments), stronger rapport between assessors and participants, better coordination among team members to reduce excessive reminder calls, and the introduction of participant assessment cards to track follow-up visits.

Although 79% of participants in both arms completed the 3-month treatment phase, adherence patterns differed by modality. Participants in the HAP arm attended most scheduled sessions, whereas those in the ADM arm consumed just over half of their prescribed doses, reflecting variable prescribing practices and participant hesitancy. In response, we increased medical officer training, worked with the state health system to authorize telemedicine prescribing by the trial psychiatrist, and clarified expectations about continuing treatment even after symptoms improved. We also introduced more flexible treatment delivery options and simplified documentation with a single patient card. Treatment fidelity in the psychotherapy arm was adequate but variable across counselors. This prompted the introduction of more targeted counselor training and greater emphasis on using fidelity reviews to guide supervision and problem-solving at the counselor level.

Study assessments achieved high completion rates and data quality, but proved burdensome to implement. The baseline battery was too long, some measures were difficult to administer, and both staff and participants found the six study assessments excessive. In response, we made several changes for the main trial, including shortening the assessment battery substantially (Pozuelo et al., 2026), refining or replacing problematic questions, and reducing follow-up assessments from six to four. We also strengthened quality control through regular assessor training, systematic review of audio-recordings, and periodic on-site checks. In addition, findings from the pilot confirmed the feasibility of collecting biological samples in primary care settings, leading to protocol refinements such as reducing blood volume requirements, adopting an improved DNA extraction method, and incorporating saliva sampling as a non-invasive alternative for the main trial.

Both HAP and ADM were associated with substantial improvements in depressive symptoms, with nearly half of the participants reaching remission and most reporting subjective improvement in health and tension.

These improvements were expected, given that both interventions are evidence-based treatments for depression (Patel et al., 2003, 2017; Weobong et al., 2017), and they provide reassurance about the quality of intervention delivery and trial procedures. Although this pilot was not powered to detect between-arm differences, variability in individual outcomes highlights the need for precision approaches. The larger OptimizeD trial is designed to move beyond average effects by identifying patient-level characteristics that can guide personalized treatment selection.

This study has limitations. First, as expected for a pilot, the small sample size was not powered to detect between-arm differences or develop precision treatment algorithms; therefore, all treatment outcome findings are descriptive only. Second, the enrollment rate was modest (42% of eligible participants), with lack of time cited as the main reason for refusal, suggesting potential recruitment challenges for scale-up. Third, the baseline assessment battery was lengthy and burdensome, and mid-treatment assessments were frequent, potentially contributing to participant fatigue and affecting data quality. Fourth, treatment implementation revealed important barriers. Medication adherence was suboptimal, with participants taking only half of the prescribed doses based on pill counts, yet we lacked systematic data on reasons for non-adherence. Some medical officers were reluctant to prescribe antidepressants to younger adults, indicating inconsistent implementation. HAP fidelity scores showed adequate but variable delivery across counselors, suggesting the need for enhanced training and supervision. Fifth, biological sampling faced multiple challenges: only 67% consented to blood draws (primarily due to needle phobia), the initial DNA extraction protocol yielded poor-quality samples requiring mid-study modification, and alternative sampling methods like saliva collection were not tested before adoption in the main trial. Sixth, acceptability was assessed through behavioral proxies (treatment adherence and retention) rather than direct self-report or qualitative data, which limits insight into participants' and providers' experiences of the study and interventions. Lastly, the absence of serious adverse events, while

positive, meant escalation protocols could not be fully tested. Despite these limitations, the pilot successfully demonstrated the feasibility of conducting a precision treatment trial for depression in Indian primary care settings and generated critical insights that directly informed protocol refinements for the larger OptimizeD trial.

Taken together, these findings support the conclusion that a precision treatment trial is feasible in this setting, following implementation of the protocol refinements identified through the pilot. Data from the ongoing main OptimizeD trial demonstrate improvements across all major feasibility domains identified during the pilot, including enrollment (70% vs. 42%), biological sample consent (97% vs. 67%), retention (90% vs. 82%), HAP session attendance (6.1 vs. 5.6 sessions), ADM dose adherence (64.2% vs. 57.9%), and HAP fidelity (mean Q-BAS score: 3.2 vs. 2.6). These findings suggest that the challenges identified during the pilot were successfully addressed before the launch of the main trial, providing confidence that it is well positioned to generate interpretable findings.

CONCLUSIONS

This pilot demonstrated that a precision treatment trial comparing psychotherapy and antidepressant medication for depression can be implemented in Indian primary care settings but identified key operational and implementation challenges and generated practical solutions that directly informed the design of the main OptimizeD trial. While both treatments were associated with symptom improvement, the variability in individual response highlights the importance of developing data-driven precision approaches to guide treatment selection. Building on these findings, the main OptimizeD trial will develop and test a contextually grounded precision treatment model with the potential to reduce the burden of trial-and-error treatment selection, improve patient outcomes, and support more efficient use of scarce healthcare resources in primary care settings.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.beth.2026.07.002.

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Ethics approval and consent to participate. The study is approved by the ethics committees of Sangath (AB-2021–69), AIIMS Bhopal (EF0237), and Harvard Medical School (IRB20-2144). 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. In addition, recruitment at the selected primary healthcare clinics was authorized by the National Health Mission, Government of Madhya Pradesh, through a project-specific MoU, and permissions granted by Bhopal's Chief Medical and Health Officer. The pilot and main trial were registered with ClinicalTrials.gov (NCT05944926 on 2 July 2023 and NCT06153004 on 22 November 2023) and with the Clinical Trials Registry–India (CTRI/2024/01/061932 on 29 January 2024). A Trial Steering Committee and an independent Data and Safety Monitoring Board oversaw study implementation. Written informed consent was obtained from all participants prior to study initiation. Participants were provided with INR 500 for each in-person study assessment as compensation for their time, along with refreshments during the visits. No additional compensation was offered for participation in the study.

Data availability. Individual participant data will be shared through the National Institute of Mental Health (NIMH) Data Archive. To ensure participant privacy and data security, all shared data will be de-identified according to established protocols and guidelines.

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