Protocol

Smartphone-Delivered Cognitive Behavioral Digital Therapeutic for Children and Adolescents With Major Depressive Disorder: Protocol for a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: Depression is a leading contributor to morbidity and disability in children and adolescents. Cognitive behavioral therapy (CBT) is a guideline-recommended first-line treatment, but access is constrained by therapist supply, distance, and stigma. Internet-based CBT is a scalable adjunct in adults, yet regulatory-grade evidence in Chinese pediatric samples remains limited.

Objective: This trial will determine whether a smartphone-delivered CBT-based digital therapeutic is superior to a matched health-education placebo in reducing depressive symptoms in Chinese children and adolescents with major depressive disorder (MDD), and characterize its safety.

Methods: This is a prospective, multicenter, double-blind, placebo-controlled superiority trial at 4 tertiary-A hospitals in mainland China. Children and adolescents aged 8-17 years meeting *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) criteria for current MDD without psychotic features and scoring above 30 on the Children's Depression Rating Scale-Revised (CDRS-R) at screening will be randomized 1:1 to the investigational digital therapeutic (Model WL-PD) or a visually matched health-education placebo. Both arms receive 8 weeks of structured content on an identical schedule; participants with CDRS-R ≥57 additionally receive open-label fluoxetine under weight-banded dosing. The primary end point is CDRS-R total-score reduction from baseline to week 8. Secondary end points include CDRS-R change at weeks 1 to 6; response and remission rates; Clinical Global Impression scores; the Children's Depression Inventory; the Conners' Parent Symptom Questionnaire; and a week-8 device-performance evaluation. Safety end points include adverse-event, serious adverse-event, and device-defect incidence. The planned sample of 214 participants (107 per arm) is powered at 80% to detect a between-arm difference of 4.6 CDRS-R points (assumed control SD 10.7) with a 1-sided α of .025 and 20% inflation for attrition. The primary analysis is an analysis of covariance on the full analysis set adjusting for baseline CDRS-R, severity category, fluoxetine exposure, and site; superiority is declared if the lower bound of the 2-sided 95% CI excludes zero, with a mixed model for repeated measures as a sensitivity analysis.

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Results: The trial opened to enrollment in March 2026; recruitment is ongoing, with a planned close in December 2026. The last week-8 visit is expected in the first quarter of 2027, and the primary analysis the following year.

Conclusions: The trial addresses 3 recognized gaps in the pediatric digital therapeutics literature: a rigorous, structurally matched blinded control condition, recruitment beyond a single site, and integration of guideline-concordant pharmacotherapy. Because recruitment is confined to tertiary hospitals and excludes participants with prominent suicidality or comorbidity, findings will apply to supervised use in specialist services rather than unselected community care.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2600120453; https://tinyurl.com/3xzaajhp

International Registered Report Identifier (IRRID): DERR1-10.2196/103430

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KEYWORDS

adolescent depression; CDRS-R; cognitive behavioral therapy; digital therapeutics; randomized controlled trial; study protocol

Introduction

Overview

Depression is a common, recurrent, and disabling psychiatric disorder, and the World Health Organization has identified it as a leading cause of disability worldwide [1]. Among adolescents, depression is one of the principal causes of morbidity and disability and a known precursor to a broader trajectory of poor mental-health, educational, and social outcomes [2]. Estimates place the prevalence of childhood depression at approximately 2.8% and adolescent depression at approximately 5.6% [3], and almost half of adolescents who recover from an index episode experience a recurrence within 5 years [4]. The clinical presentation in younger patients differs from that in adults: irritability, low frustration tolerance, sleep and appetite disturbance, and somatic complaints are common, often co-occurring with elevated suicide risk and impaired academic and social functioning. Early, evidence-based treatment is therefore essential to reduce both the immediate symptom burden and the longer-term developmental consequences of pediatric depression. In China, depression among children and adolescents has been identified as a growing public-health concern, with national reporting drawing attention to the burden carried by school-age populations and to the gap between the number affected and the specialist treatment capacity available [5].

The current Chinese Guidelines for the Prevention and Treatment of Depressive Disorders (2025 edition) recommend a stepped-care approach in which mild pediatric depression is treated first with psychotherapy and moderate to severe presentations are treated with antidepressant pharmacotherapy, with cognitive behavioral therapy (CBT) and interpersonal psychotherapy adapted for adolescents (IPT-A) listed as the recommended psychotherapies [6]. Approved antidepressant pharmacotherapy options for this age group remain narrow: in China, only fluoxetine (≥8 years) and sertraline (≥6 years) carry a 1A recommendation, and in the United States the US Food and Drug Administration has approved fluoxetine (≥8 years) and escitalopram (≥12 years) for pediatric major depressive disorder (MDD) [6]. Despite the availability of guideline-concordant psychotherapy, real-world delivery is constrained by therapist supply, geographic distance, scheduling demands on school-age patients, and stigma associated with attending in-person mental-health services.

Digital therapeutics (DTx) are software products that deliver evidence-based clinical interventions for the prevention, management, or treatment of disease. By standardizing and digitizing established psychotherapy protocols and augmenting them with multimedia and gamification elements, DTx can extend access to the most evidence-supported components of CBT while improving patient engagement and adherence. Internet-delivered CBT (iCBT) is the most extensively evaluated DTx modality for depression. An individual-patient-data network meta-analysis of guided and unguided iCBT in adult depression showed that both formats outperformed control conditions (waitlist, treatment-as-usual, attention control) on the 9-item Patient Health Questionnaire (PHQ-9) in the short and long term, with guided iCBT showing additional advantage over unguided iCBT [7]. An earlier network meta-analysis of CBT delivery formats found no significant effectiveness differences between individual, group, telephone, and guided self-help formats, although unguided self-help did not significantly outperform care-as-usual and showed lower acceptability than supported formats [8]. The 2025 Chinese guideline accordingly endorses iCBT as a stand-alone option for mild depression and as an adjunct for moderate to severe presentations, particularly when patients are unable to access traditional in-person CBT [6].

Pediatric and adolescent evidence remains comparatively sparse, although it has grown substantially over the past decade. A meta-analysis of technology-delivered interventions in children and adolescents identified 34 randomized trials and found a medium pooled effect for CBT-based programs relative to control conditions [9], and an adolescent-specific systematic review and meta-analysis of computerized CBT reported small but statistically significant reductions in both depression and anxiety symptoms, with effects comparable to active interventions such as face-to-face therapy or treatment as usual [10]. Evidence for standalone smartphone applications is more modest: a meta-analysis of apps used without professional support found a significant but small effect on depressive symptoms and concluded that unsupported apps cannot yet be recommended as stand-alone psychological treatment [11], which supports the prescription-mediated, clinician-supervised model adopted here. Among individual pediatric programs,

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SPARX, a gamified computerized CBT intervention, was noninferior to treatment as usual in help-seeking adolescents in New Zealand primary care [12], and the Think, Feel, Do program produced encouraging preliminary outcomes in a small pilot trial [13]. Both CBT and interpersonal psychotherapy are supported as first-line psychotherapies for pediatric depression by network meta-analysis [14].

The most directly relevant precedent for the present design is a double-blind randomized placebo-controlled pilot trial of a computer-based CBT program ("The Journey") in adolescents with depressive symptoms, conducted in New Zealand, in which the iCBT group showed a substantially greater Children's Depression Rating Scale-Revised (CDRS-R) improvement than a structurally matched health-education placebo (between-arm difference of approximately 11 CDRS-R points; $P<.001$) [15]. That study established the feasibility of structurally matched placebo software as a credible comparator for pediatric digital therapeutics.

The present trial is distinguished from these precedents on 6 dimensions. First, delivery platform: the intervention is a smartphone-delivered, prescription-only software-as-a-medical-device, whereas most prior pediatric programs were computer- or web-based and available without prescription. Second, diagnostic inclusion: participants must meet *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) criteria for current MDD confirmed by structured diagnostic interview, whereas several precedents enrolled adolescents with self-reported depressive symptoms rather than a confirmed disorder. Third, clinician supervision: treatment is prescribed and monitored by a designated clinician through a paired dashboard, in contrast to self-guided or minimally supported programs. Fourth, comparator design: the comparator is a structurally matched, visually identical placebo application supporting a genuinely double-blind evaluation, rather than a waitlist or treatment-as-usual control. Fifth, regulatory purpose: the trial is designed to registration standard to support a marketing application to the Chinese National Medical Products Administration. Sixth, cultural and health-system setting: recruitment is from tertiary-care pediatric psychiatric services in mainland China, a population and care context for which the authors are not aware of a comparable prior evaluation. To the authors' knowledge, this is among the first registration-grade randomized controlled trials of a smartphone-delivered DTx for pediatric MDD conducted in a Chinese population. The trial described in this protocol is intended to address that gap.

The investigational device—Depressive Symptoms Psychological Therapy and Rehabilitation Training Software (Model WL-PD; Beijing Wangli Medical Technology Co, Ltd)—is a prescription-only, smartphone-delivered software-as-a-medical-device that combines content elements drawn from CBT, interpersonal psychotherapy, and behavioral activation, delivered to children and adolescents through an interactive multimedia interface and supervised by a prescribing clinician through a paired clinician-side dashboard.

Objectives and Hypotheses

The primary objective is to confirm whether the investigational software is superior in efficacy to a structurally matched health-education placebo application for the treatment of pediatric MDD, indexed by week-8 change in CDRS-R total score, and to characterize its safety profile in supervised use within specialist pediatric mental-health services. The corresponding statistical hypotheses are H0: $\mu test - \mu control \leq 0$ (no superior change) vs H1: $\mu test - \mu control > 0$ (greater change in the test arm), tested at a 1-sided α of .025. Secondary objectives are to characterize the longitudinal trajectory of symptom change across the 8-week treatment period; to estimate response and remission rates over time; to evaluate clinician- and parent-reported global impression and behavioral symptomatology; and to evaluate device usability and user experience.

Methods

Patient and Public Involvement

No patients or members of the public were involved in the design, conduct, or reporting of this trial, or in the development of the research question or outcome measures.

Trial Design

The trial is a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group superiority trial evaluating an investigational smartphone-delivered digital therapeutic against a structurally matched health-education placebo application in children and adolescents with current MDD. The protocol (sponsor identifier BJWL-202512, version V1.1, dated January 26, 2026) was developed in accordance with the Chinese Good Clinical Practice for Medical Device Clinical Trials, the Chinese guideline on Medical Device Clinical Trial Design Principles, and the relevant chapters of International Council for Harmonisation guidances E9 (statistical principles) and E10 (choice of control group). The study is registered with the Chinese Clinical Trial Registry under identifier ChiCTR2600120453 (prospective registration; date of registration March 16, 2026); registration was completed before recruitment opened and before the first participant was enrolled, satisfying the criterion for prospective registration.

The trial is being conducted at 4 tertiary-A hospitals: Peking University Sixth Hospital (Beijing)—coordinating center, The First Hospital of Hebei Medical University (Hebei), The Fourth People's Hospital of Hefei (Anhui), and The Fifth Affiliated Hospital, Sun Yat-sen University (Guangdong). The coordinating investigator is JL of Peking University Sixth Hospital and oversees day-to-day trial conduct in coordination with the principal investigators at the 4 participating sites. The protocol underwent a single revision (V1.0 → V1.1) following review comments from the lead-site ethics committee. Subsequent substantive amendments will be reported in the trial master file and, where they affect interpretation, in the results manuscript.

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Participants

Eligible participants are children and adolescents aged 8-17 years (inclusive), of any sex, who meet *DSM-5* criteria for current MDD (single or recurrent episode, without psychotic features) confirmed by the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL) [16]; who score greater than 30 on the CDRS-R [17] at screening; who are proficient in smartphone use; and whose participation, together with that of their legal guardian, is documented through written informed assent and consent.

Exclusion criteria are (1) any current psychiatric disorder other than depression; (2) prior failure of a documented adequate trial of 1 antidepressant medication; (3) prominent suicidal ideation or behavior, defined as a score greater than 4 on CDRS-R item 13; (4) clinically significant unstable cardiovascular, hepatic, renal, hematological, endocrine, or oncological disease; ophthalmic disease precluding sustained use of an electronic display; or thyroid disease (thyroid-stimulating hormone above the laboratory upper limit of normal at screening), or hyper- or hypothyroidism in the investigator's clinical judgment, with a single retest permitted within the screening window); (5) history of seizures (excluding pediatric febrile convulsions); (6) intellectual disability, language comprehension or expression impairment, sensory impairment, or motor impairment that would preclude cooperation with treatment; (7) any antidepressant herbal therapy or nonpharmacological depression intervention (modified electroconvulsive therapy, transcranial magnetic stimulation, biofeedback, light therapy, acupuncture, or systematic psychotherapy) within the 3 months preceding screening; (8) a stated unwillingness to engage with psychotherapy or a stated belief that psychotherapy is ineffective; (9) a positive pregnancy test; (10) inadequate antidepressant washout (less than 4 weeks for fluoxetine; less than 2 weeks for any other antidepressant) prior to screening; (11) participation in any other drug or device clinical trial in the preceding 3 months; or (12) any other condition that, in the investigator's judgment, renders the participant unsuitable for the trial.

Recruitment

Participants are recruited at the 4 participating tertiary-A hospitals, each providing specialist psychiatric services. The principal investigator at each site is responsible for site-level enrollment and may delegate recruitment, informed consent, screening, and follow-up activities to qualified study staff designated on the site delegation log, in accordance with the principal-investigator responsibilities specified in the Chinese Good Clinical Practice for Medical Devices.

Withdrawal, Discontinuation, and Retention

Participants and their guardians retain the right to withdraw from the trial at any time and without prejudice to ongoing clinical care. Investigator-initiated discontinuation may occur in cases of refusal of further treatment or follow-up; loss to follow-up; poor adherence; nonanticipated or serious adverse events (SAEs) that, in the investigator's judgment, render continued participation unsafe; or sponsor-identified safety or eligibility concerns. For every participant who is withdrawn or lost to follow-up, the investigator documents the date and reason, attempts (where the participant or guardian consents) to complete an off-treatment assessment, and ensures continued clinical care for any preexisting or treatment-emergent condition. Participants who withdraw before first treatment exposure retain their randomization number, which is not reissued.

Strategies to support retention follow protocol §10.2 and include thorough informed consent and pretreatment education to ensure participants and guardians understand the trial requirements; periodic subjective and objective assessment of symptom trajectory at every visit, so that participants whose depression is not improving receive timely reevaluation rather than delayed action; and active clinical management to minimize the likelihood that participants withdraw because of inadequate or delayed care.

Ethical Considerations

The protocol, the participant- and guardian-facing informed consent and assent forms, and the supporting study documents were reviewed and approved by the Medical Ethics Committee of Peking University Sixth Hospital (Institute of Mental Health; approval reference 2026, Lun Shen number 13; date of approval February 13, 2026) prior to recruitment. Site-level ethics review was obtained at each participating center before that center opened to enrollment. Substantive amendments to the protocol, the informed consent and assent forms, or other participant-facing material require ethics committee approval before implementation; minor administrative changes are reported for the committee's records. The conduct of the trial is governed by the Declaration of Helsinki and by the applicable Chinese laws and regulations on medical device clinical research.

Two age-banded informed consent and assent documents are used: a guardian consent form for the legal guardian of every participant, and an age-appropriate assent form for participants aged 8-17 years. Both documents are signed and dated by the participant (where competent) and the guardian, and countersigned by the investigator; one copy is retained by the participant and one filed with the trial source documents. For participants who lack reading capacity, an impartial witness is present for the entire informed-consent discussion and countersigns the consent record. Participants and guardians are informed of their right to withdraw at any time and without prejudice to ongoing clinical care. English translations of the informed consent and assent forms are provided in Multimedia Appendix 1.

Randomization and Blinding

Eligible participants are allocated 1:1 to the investigational or placebo arm by a central electronic data capture (EDC)–based randomization service. The randomization sequence is generated with SAS software (version 9.4 or later; SAS Institute) by the trial statistician. Once eligibility is confirmed in the EDC, the system returns an activation code; the device administrator at each site uses the activation code to provision a participant account in the clinician-side dashboard, and the participant downloads the trial-specific mobile app and enters the code to

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activate their assignment. The activation code is the only identifier that links the participant to a treatment assignment; participants who are randomized but discontinue prior to first treatment exposure retain their allocated number, which is not reissued to subsequent participants. The investigational software and the placebo software are delivered through a single mobile app whose user-facing interface, navigation, copy, and visual style are identical between arms. Group differentiation is implemented entirely on the back end and is bound to the activation code. Investigators, participants, guardians, and outcome assessors are all blinded to allocation; in the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [18]/CONSORT (Consolidated Standards of Reporting Trials) vocabulary [19], this corresponds to a double-blind design with blinded outcome assessment. Site device administrators are responsible for activation-code management, are functionally separated from outcome assessment, and do not communicate allocation status to investigators or participants. Unblinding is permitted only where it is necessary for the safe management of an SAE and is documented in the trial master file together with the rationale and the time of unblinding.

Interventions

Investigational Arm

The investigational arm receives the Depressive Symptoms Psychological Therapy and Rehabilitation Training Software (Model WL-PD, release version 1). The product is registered to and sponsored by Beijing Wangli Medical Technology Co, Ltd (the industry sponsor of this trial), and is manufactured under contract by Sichuan Wangli Medical Technology Co, Ltd, a related corporate entity. The placebo software used in the comparator arm is manufactured by the same contract manufacturer; this corporate relationship is acknowledged among the trial's competing-interest disclosures. The software is a smartphone-delivered digital therapeutic combining CBT, interpersonal psychotherapy, and behavioral activation and is delivered through a hybrid architecture comprising a patient-facing mobile app, a clinician-facing web dashboard, and a back-end server. Therapeutic content is organized into 8 sequential treatment stages of 7 sessions each, totaling 56 sessions across 8 weeks of structured intervention; a session unlocks only after the preceding session has been completed and the next scheduled date has arrived, and in stages 6 to 8 the seventh session is a consolidation and review session. Treatment material is delivered through text, audio, video, image, table, and gamified-training modalities and is intended to address depressive symptomatology across cognitive, emotional, behavioral, and interpersonal domains.

The product is intended for prescription-mediated use in children and adolescents diagnosed with depressive symptoms, with the prescribing clinician providing supervision and progression review through the clinician-side dashboard. Use is permitted in either home or health care–facility settings.

CBT is the primary theoretical framework of the investigational software. The curriculum follows a conventional CBT sequence—psychoeducation and goal setting, emotion identification and regulation, identification and restructuring of automatic thoughts, attribution training, behavioral activation and values clarification, problem-solving, and finally modification of intermediate and core beliefs—and incorporates adjunctive interpersonal-psychotherapy elements (interpersonal cycles, communication skills, and family interaction) and behavioral-activation components at defined points in that sequence. The title and abstract accordingly describe the product as a CBT-based digital therapeutic, with interpersonal and behavioral-activation content as adjunctive rather than coequal frameworks. The stage-by-stage therapeutic focus of each arm is summarized in Table 1, and the intervention is described below following the Template for Intervention Description and Replication (TIDieR) [20].

Following the TIDieR framework, the intervention is characterized as follows. *Materials and procedures*: standardized digital therapeutic content delivered as text, audio, video, image, table, and gamified training modules through the patient-facing application, with the curriculum fixed in software and identical for all participants. *Who provides*: a designated treating clinician prescribes the software and supervises progression; the therapeutic content itself is delivered by the software rather than by a therapist. *How and where*: individually, on the participant's own smartphone, in home or health care–facility settings. *When and how much*: 8 stages of 7 sessions over 8 weeks (56 sessions), with each session unlocking only after completion of the preceding session and arrival of the scheduled date, so that exposure is paced uniformly. *Tailoring*: the sequence and content are fixed; the clinician may suspend, resume, or terminate the course on clinical grounds. *Fidelity*: delivery fidelity is invariant because the content is standardized software rather than therapist-delivered material; receipt is verified objectively through back-end logging of stage progression, with attainment of stage 6 prespecified as the planned therapeutic dose; and every clinician action on the dashboard is recorded with operator identity, action type, and time stamp, providing an auditable record of supervision.

Clinician supervision operates through the paired dashboard as follows. Each participant is assigned a designated treating clinician who reviews the dashboard at the protocol-mandated minimum time points corresponding to the in-person visits at weeks 2, 4, and 8, and who reexamines recent data immediately before each clinical interview. The dashboard displays course and stage progression, same-day task completion, recent change in in-app self-assessment results, the time of first application launch each day, and cumulative usage duration. Consecutive nonuse, declining task completion, or marked deterioration in self-assessment prompts further manual clinical evaluation, and the clinician may suspend, resume, or terminate the treatment course on the basis of clinical judgment. The dashboard supports monitoring of engagement, adherence, and treatment fidelity; it does not generate automated risk alerts, and it does not substitute for the clinical safety monitoring described below.

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Table 1. Stage-by-stage content of the investigational software and the health-education placebo. Both arms deliver 8 sequential stages of 7 sessions each (56 sessions in total) on an identical unlocking schedule and through an identical interface; in stages 6 to 8, the seventh session of the investigational curriculum is a consolidation and review session. The placebo delivers general adolescent health education and contains no cognitive behavioral, interpersonal, or behavioral-activation change techniques and no individualized therapeutic progression.

Week	Investigational software (therapeutic focus)	Health-education placebo (topic)
Week 1	CBT orientation; problem and goal list; 4-element model (fact, thought, emotion, behavior); awareness of somatic symptoms; nonsuppression of emotion	Health and exercise
Week 2	Emotion identification, acceptance and regulation; action points and opposite action; relaxation techniques; environment and habit change; meaningful activity	Sleep
Week 3	Identification of unhelpful automatic thoughts (catastrophizing, overgeneralization, and absolutist thinking); cognitive restructuring by evidence-finding and decatastrophizing; coping with distraction	Healthy living and safety awareness
Week 4	Attribution training (6 attribution types; positive vs negative attribution); resolving common attribution pitfalls; goal review; coping with loneliness and peer pressure	Hygiene and health care
Week 5	Behavioral activation (activity scheduling, pleasure-rating bias); values clarification; sleep improvement; autonomy and collaboration with parents; building self-confidence	Growth and development
Week 6	Problem-solving technique; rational decision-making; trauma response; interpersonal cycles; causes of poor communication; nonviolent communication; consolidation review	Nutrition
Week 7	Consolidation of behavioral techniques; intermediate beliefs (concept, identification, and 4-step modification); family interaction, including expressing gratitude and shared interests; consolidation review	Health life skills
Week 8	Core-belief identification and modification; interaction of core beliefs, intermediate beliefs, and automatic thoughts; positive self-concept; future planning; course summary and review	Disease awareness and prevention

Comparator Arm

The comparator arm receives the Health Education Placebo Software (release version 1; Sichuan Wangli Medical Technology Co, Ltd). The placebo software follows a matched 8-stage, 7-session schedule delivered through an interface visually identical to the investigational software. Its content comprises general adolescent health education—physical activity, sleep hygiene, personal safety, hygiene and health care, growth and development, nutrition, health life skills, and disease prevention—delivered as structured video modules on the same 8-stage, 7-session schedule as the investigational arm (Table 1). Critically, the placebo contains none of the active therapeutic components of the investigational software: no cognitive restructuring, no behavioral activation, no interpersonal problem-solving, no belief modification, and no individualized therapeutic progression. What the 2 arms share is the nonspecific apparatus of treatment—an identical user interface, navigation, and visual style; the same weekly cadence and session-unlocking logic; the same requirement for sustained engagement; and the same clinician supervision through the dashboard. The experimental contrast therefore isolates the specific therapeutic content rather than the effects of digital engagement, structure, or clinical attention.

The selection of a structurally matched placebo application as the comparator follows the precedent established by Stasiak and colleagues [15] for adolescent computer-based CBT, the absence of an approved comparator product on the Chinese market, and the recommendation in the Chinese Medical Device Clinical Trial Design Principles to select a placebo of comparable form when an active comparator is not feasible. This design controls for the nonspecific therapeutic effects of digital engagement and supervised use.

Treatment credibility and outcome expectancy are controlled by design rather than by measurement. Because the two applications are visually and structurally indistinguishable, allocation is concealed behind a backend activation code, and participants, guardians, investigators, and outcome assessors are all blinded, differential expectancy between arms is minimized at source. Engagement is measured objectively in both arms through back-end logging of progression through the 8-stage curriculum, and stage-completion data will be reported by arm alongside the prespecified adherence definition. No separate credibility or expectancy questionnaire is administered; this is acknowledged among the limitations.

Concomitant Pharmacotherapy

Both arms permit guideline-concordant open-label antidepressant pharmacotherapy where indicated by baseline severity: participants meeting the moderate to severe severity criterion (CDRS-R ≥57) [21,22] receive fluoxetine hydrochloride tablets (10 mg) according to standardized weight-banded dosing. Adolescents aged 12-17 years start at 10 mg/day for 1 week, then 20 mg/day through the end of the trial, and children aged 8-11 years start at 5 mg/day for 1 week, then 10 mg/day through the end of the trial. Dose adjustments based on individual response, body weight, and tolerability are at the investigator's discretion and are documented in the case report form. Participants with mild baseline severity (CDRS-R below 57) receive the assigned digital intervention without concomitant pharmacotherapy.

For severe insomnia, short-term hypnotic use (zolpidem, zopiclone, eszopiclone, or zaleplon at labeled doses, for no more than 2 consecutive weeks and no more than 4 weeks in total, withheld for at least 8 hours before any scheduled assessment) is permitted and recorded. The following classes are prohibited for the duration of the trial: antipsychotic medications (eg, chlorpromazine, haloperidol, clozapine, perphenazine, sulpiride,

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olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, paliperidone, and amisulpride); mood stabilizers (eg, lithium carbonate, valproate, carbamazepine, lamotrigine, and gabapentin); benzodiazepine anxiolytics (eg, alprazolam, diazepam, lorazepam, oxazepam, and clonazepam); other agents with sedative or hypnotic action used adjunctively for anxiety, including melatonin; herbal antidepressants; and any nonpharmacological depression intervention other than the assigned study intervention (including modified electroconvulsive therapy, transcranial magnetic stimulation, biofeedback, light therapy, acupuncture, and any systematic psychotherapy).

A participant is considered to have received the planned dose of the digital intervention if they reach stage 6 of the 8-stage curriculum (ie, 75% of the structured content). This threshold is used both as the per-protocol completeness criterion and as the per-participant adherence definition referenced in the analysis-population specification.

Outcomes

Primary Outcome

The primary outcome is the reduction in CDRS-R total score from baseline to week 8, computed as the screening-baseline CDRS-R total minus the week-8 CDRS-R total, so that a larger positive value indicates greater improvement; the same sign convention is used throughout, and the superiority hypothesis (H1: μtest – μcontrol >0) is therefore expressed in terms of this reduction. The CDRS-R [17] is a clinician-administered, 17-item, semistructured rating scale that yields a continuous total score in which higher scores reflect more severe depressive symptomatology. The version used in this trial is the one validated for pediatric and adolescent samples [21]; the CDRS-R is the conventional primary efficacy measure in pediatric antidepressant and psychotherapy trials in this age group [23,24].

Secondary Outcomes

Prespecified secondary efficacy outcomes are change in CDRS-R total from baseline at weeks 1, 2, 3, 4, and 6; treatment response rate, defined as a CDRS-R reduction of at least 30% from baseline, evaluated at weeks 1, 2, 3, 4, 6, and 8; remission rate, defined as a CDRS-R total of 28 or below, evaluated at the same time points; Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I) [25] at weeks 2, 4, and 8; change in the self-reported Children's Depression Inventory (CDI) [26] total from baseline at weeks 2, 4, and 8; change in the parent-reported 48-item Conners' Parent Symptom Questionnaire (PSQ) [27,28] total from baseline at weeks 2, 4, and 8; and a week-8 device-performance evaluation comprising investigator-elicited ratings of interface clarity, usability, and intent to continue use (categorized as excellent, good, average, or poor; the device-performance "good-or-better" rate is the count of excellent and good ratings divided by the total number of evaluations).

Safety Outcomes

Prespecified safety outcomes are adverse event incidence and count (overall and device-related); SAE incidence and count (overall and device-related); device defect incidence and count. Adverse events are recorded throughout the on-treatment and follow-up periods. Events are graded for severity and assessed for relatedness to the investigational device using the 4-level scheme (definitely related, possibly related, possibly unrelated, and definitely unrelated) specified in the National Medical Products Administration (NMPA) 2022 Notice No. 21, Annex 5. Device defects (eg, labeling errors, software faults, and performance failures) are recorded separately and reported in parallel with the adverse-event channel.

Schedule of Assessments

The schedule of assessments comprises 1 combined screening and baseline visit (V1; no separate randomization visit, with randomization performed at the end of V1 once eligibility is confirmed) and 6 on-treatment visits (Table 2). Visits V1, V3, V5, and V7 are conducted in person at the site, while V2, V4, and V6 are conducted by video. The week-8 visit (V7) carries a positive-only window of 7 days to accommodate the asymmetric scheduling of the primary end point.

Biological specimens (blood samples for complete blood count and hepatic, renal, and thyroid biochemistry; urine samples for pregnancy testing in menarcheal participants aged 12 years or older) are collected at site laboratories solely for the protocol-specified safety assessments. Specimens are processed locally, results are recorded in the electronic case report form (eCRF), and residual material is destroyed after analysis. No samples are stored, banked, or used for ancillary or future research, and consent for such uses is therefore not requested.

At V1, eligibility is confirmed through history-taking, vital-sign measurement, 12-lead electrocardiography, complete blood count, hepatic and renal biochemistry, thyroid function (free triiodothyronine, free thyroxine, thyroid-stimulating hormone), and urine or serum pregnancy testing for menarcheal participants aged 12 years or older. Diagnostic confirmation by K-SADS-PL and baseline rating-scale administration (CDRS-R, CGI-S, CDI, and PSQ) are completed before randomization. Vital signs and electrocardiography are repeated at V3, V5, and V7; laboratory and pregnancy testing are repeated at V7. CDRS-R is administered at every visit. CDI and PSQ are administered at V1, V3, V5, and V7; CGI-S at V1, V3, V5, and V7; CGI-I at V3, V5, and V7. Device-performance evaluation is conducted at V7. Adverse events, device defects, and concomitant therapy are recorded at every visit. Participant diary cards are issued at V1, V3, and V5 and collected at V3, V5, and V7. Unscheduled visits may be added at the investigator's discretion in response to safety signals or laboratory abnormalities and are recorded in the case report form. The schedule of enrollment, interventions, and assessments is summarized in Table 3, following the SPIRIT recommendation.

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Table 2. Schedule of trial visits.

Visit	Label	Window	Mode
V1	Screening/baseline	Day –7 to day 0	In-person
V2	Week 1	±2 days	Video
V3	Week 2	±2 days	In-person
V4	Week 3	±2 days	Video
V5	Week 4	±3 days	In-person
V6	Week 6	±3 days	Video
V7	Week 8	+7 days	In-person

Table 3. Schedule of enrollment, interventions, and assessments (SPIRIT [Standard Protocol Items: Recommendations for Interventional Trials]). The digital intervention, concomitant pharmacotherapy where indicated, and the recording of adverse events, device defects, and concomitant therapy continue across the 8-week treatment period; checkmarks for these rows indicate the visits at which status is reviewed and documented.

Procedure	V1 (baseline)	V2 (week 1)	V3 (week 2)	V4 (week 3)	V5 (week 4)	V6 (week 6)	V7 (week 8)
Informed consent/assent	✓						
Eligibility assessment	✓						
K-SADS-PL[a] diagnostic confirmation	✓						
Demographics and medical history	✓						
Randomization	✓						
Digital intervention (both arms)	✓	✓	✓	✓	✓	✓	✓
Open-label fluoxetine (if indicated)	✓	✓	✓	✓	✓	✓	✓
CDRS-R[b]	✓	✓	✓	✓	✓	✓	✓
CGI-S[c]	✓		✓		✓		✓
CGI-I[d]			✓		✓		✓
CDI[e]	✓		✓		✓		✓
PSQ[f]	✓		✓		✓		✓
Vital signs	✓		✓		✓		✓
12-lead electrocardiography	✓		✓		✓		✓
Hematology and biochemistry	✓						✓
Thyroid function	✓						
Pregnancy test (menarcheal, ≥12 years)	✓						✓
Device performance evaluation							✓
Adverse events	✓	✓	✓	✓	✓	✓	✓
Device defects	✓	✓	✓	✓	✓	✓	✓
Concomitant therapy	✓	✓	✓	✓	✓	✓	✓
Diary card issued	✓		✓		✓		
Diary card collected			✓		✓		✓

[a]K-SADS-Pl: Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version.

[b]CDRS-R: Children's Depression Rating Scale-Revised.

[c]CGI-S: Clinical Global Impression-Severity.

[d]CGI-I: Clinical Global Impression-Improvement.

[e]CDI: Children's Depression Inventory.

[f]PSQ: Conners' Parent Symptom Questionnaire.

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Sample Size

The sample size was calculated under a parallel-group superiority framework following Annex 2 of the Chinese Medical Device Clinical Trial Design Principles, with the between-arm difference and SD assumptions drawn from the broader pediatric and adolescent CBT literature; values were set conservatively relative to the larger between-arm difference observed in the most directly comparable adolescent computer-based CBT placebo-controlled trial [15]. Under an assumed between-arm difference of 4.6 CDRS-R points, an assumed control-arm SD of 10.7, a 1-sided α of .025 (corresponding to a 2-sided α of .05), and a target power of 80%, the calculation yields 85 evaluable participants per arm (170 total). Inflating for an anticipated 20% attrition rate yields the planned enrollment of 107 per arm and 214 overall. Site-level enrollment is monitored to maintain balance across the participating centers, with a single-center cap of 50% of the total sample. A sensitivity analysis of the sample-size assumptions is provided in Multimedia Appendix 2.

Statistical Analysis

Three analysis sets are prespecified. The full analysis set (FAS) comprises all randomized participants who received at least 1 treatment exposure and who contributed at least 1 postbaseline efficacy assessment. The per-protocol set (PPS) is a subset of the FAS comprising participants who completed the primary efficacy assessment, who reached stage 6 or higher of the digital curriculum, and who incurred no major protocol violations affecting the primary end point (the complete, prespecified list of major protocol violations is held in the statistical analysis plan). The safety set comprises all randomized participants who contributed at least 1 postbaseline safety assessment. The primary efficacy analysis is conducted on the FAS, with a parallel PPS analysis as a supplementary check; baseline characteristics are summarized on the FAS; safety analyses are conducted on the safety set.

The primary efficacy analysis is an analysis of covariance on the week-8 reduction in CDRS-R total score, with treatment group as a fixed factor and the covariates specified below, assuming equal within-arm residual variance. Superiority is concluded when the lower bound of the 2-sided 95% CI for the between-arm difference (investigational minus comparator) exceeds zero. A mixed model for repeated measures (MMRM), including treatment, visit, the treatment-by-visit interaction, the same covariates, and a random participant effect, provides a sensitivity analysis. Least-squares means and the corresponding 95% CI for the week-8 between-arm contrast are reported, with superiority again indexed to the lower-bound criterion.

Because guideline-concordant open-label fluoxetine is administered to participants with moderate to severe depression in both arms, and because recruitment is distributed across 4 centers, the primary model adjusts for the principal sources of confounding in addition to the baseline score. Specifically, the analysis of covariance includes treatment group as the factor of interest and baseline CDRS-R total, baseline severity category (mild vs moderate to severe, defined by the CDRS-R threshold of 57), fluoxetine exposure, and site as covariates; the MMRM carries the same covariate set alongside visit and the treatment-by-visit interaction. Baseline characteristics, including severity category and fluoxetine exposure, are summarized by arm so that any residual imbalance is transparent. Randomization itself is unstratified simple 1:1 central allocation as originally specified: because enrollment began in March 2026, introducing stratified allocation during conduct would apply different randomization procedures to participants enrolled before and after the change without improving comparability for those already enrolled, so confounding is addressed analytically rather than by altering the allocation sequence midtrial. Beyond these prespecified adjustments, no subgroup analyses are prespecified; any such analyses undertaken would be exploratory and identified as such. The covariate set described here strengthens the model specified in protocol version V1.1, which adjusted for baseline CDRS-R alone; the additional covariates were introduced in response to peer review, before database lock and before any efficacy analysis, and will be fixed in the statistical analysis plan. No outcome definition, eligibility criterion, or allocation procedure has been altered.

For continuous secondary outcomes, between-arm comparisons use the *t* test or the Wilcoxon rank-sum test according to distributional features, with MMRM as a sensitivity analysis where the longitudinal structure permits. Binary outcomes (response and remission) are compared using the chi-square test or Fisher exact test as appropriate. Ordinal outcomes (CGI-I) are compared using the Wilcoxon rank-sum or Cochran-Mantel-Haenszel test. Within-arm pre-post comparisons use the paired *t* test or the Wilcoxon signed-rank test. Unless otherwise specified, all hypothesis tests are 2-sided at α=.05.

Missing values for the primary efficacy outcome are imputed by last observation carried forward (LOCF); the MMRM sensitivity analysis uses observed data without imputation. Outliers and out-of-range values are addressed through standardized data-cleaning queries and are not removed without documented rationale.

No interim efficacy or futility analyses are planned, and no statistical stopping boundary is therefore defined. The protocol does prespecify criteria for terminating the trial on nonstatistical grounds: a determination that the investigational device lacks clinical value; a material error in the trial protocol that precludes evaluation of the device effect; a serious deviation in conduct that precludes such evaluation; a request from the sponsor; an order from the NMPA; or a decision by the ethics committee to protect participants' rights and interests. On termination, no further participants are enrolled; participants already enrolled are assessed and followed according to arrangements agreed between the sponsor and the investigators, a safety follow-up assessment is conducted, and the investigator notifies the ethics committee. Individual-participant discontinuation criteria, including those triggered by clinically significant suicidal ideation or behavior, are described in the safety section above. Trial conduct, safety, and recruitment progress are reviewed at the coordinating-center and sponsor levels through the standing monitoring and pharmacovigilance arrangements described below, and independently by the medical safety monitor, who may recommend suspension or termination on safety grounds;

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emergent safety signals or operational concerns trigger ad hoc review independent of any prespecified analysis schedule.

All analyses will be conducted in SAS (version 9.4 or later). The full statistical analysis plan, including the operational definitions of protocol deviation and the handling of intercurrent events, will be finalized before database lock and will be filed with the trial master file.

Suicide-Risk Monitoring and Safety Management

Overview

Because the trial enrolls children and adolescents with MDD, uses a placebo-controlled design, delivers part of the intervention remotely, and administers open-label fluoxetine to participants with moderate to severe severity, the safety plan is specified operationally.

Entry Safeguards

Participants with prominent suicidal ideation or behavior, indexed by a CDRS-R item-13 score above 4, are excluded at screening. Recruitment is restricted to tertiary-A hospitals providing specialist child and adolescent psychiatric services.

Ongoing Assessment

The CDRS-R, which includes item 13 on suicidal ideation, is administered by a trained clinician at every visit (V1 through V7), and the item-13 response is reviewed in real time by the investigator rather than only at analysis. Suicide risk is determined by this item together with the investigator's global clinical assessment at each visit; all 7 visits are conducted by psychiatrists. A separate structured suicide-risk instrument is not administered, and this is acknowledged among the limitations.

Monitoring Between Scheduled Visits

The visit schedule interleaves in-person and video contacts at weeks 1, 2, 3, 4, 6, and 8, so that scheduled clinician contact occurs at intervals of approximately 1 to 2 weeks throughout the treatment period. At consent, participants and guardians are instructed to contact the site investigator without delay if symptoms worsen, and the protocol permits unscheduled visits at the investigator's discretion in response to any safety concern or laboratory abnormality. The clinician dashboard supports monitoring of engagement and adherence but does not generate automated risk alerts and is not relied upon for safety surveillance.

Escalation and Guardian Notification

When symptom deterioration or suicide risk is identified, a standard procedure common to all participating sites is followed: the clinical rater contacts the participant's guardian through the study coordinator on the same day, communicates the required clinical measures, documents the contact in that day's visit record, and files an adverse-event or serious-adverse-event report according to the assessed level of risk. Further clinical evaluation by the site psychiatrist follows, with referral to acute psychiatric services where indicated.

Clinical Rescue and Individual Discontinuation

Rather than a fixed numerical worsening threshold, clinical rescue and discontinuation are triggered by the investigator's clinical judgment, specifically the emergence of clinically significant suicidal ideation or suicidal behavior. In such cases, the study intervention is discontinued, the participant is referred for appropriate acute care, and clinical management continues through the standing services of the participating site irrespective of trial participation. Worsening depression that does not meet this threshold is managed through unscheduled visits, adjustment of guideline-concordant care, and, where the investigator judges continued participation unsafe, withdrawal under the criteria described above.

Independent Safety Oversight

An independent medical safety monitor has been appointed for the trial: a senior child and adolescent psychiatrist who is not an investigator at any participating site, who has no role in recruitment, outcome assessment, or statistical analysis, and who has no financial or professional relationship with the industry sponsor. The monitor receives all SAEs and all suicide-related events on an ongoing basis, reviews cumulative safety information, and has the authority to request additional information, to recommend protocol modification, and to recommend suspension or termination of the trial on safety grounds. Recommendations are transmitted to the coordinating investigator, the industry sponsor, and the lead-site ethics committee, and the monitor's remit is documented in an appointment charter filed with the trial master file. A full data and safety monitoring committee was judged disproportionate for this risk profile: each participant is exposed for only 8 weeks, participants with prominent suicidality are excluded at entry, no interim efficacy analysis is performed, and fluoxetine is administered open-label under guideline-concordant pediatric dosing rather than as a blinded investigational agent. Fluoxetine is the only antidepressant with demonstrated efficacy over placebo in pediatric MDD in network meta-analysis [29] and is the agent carrying a 1A recommendation in the Chinese guideline for this age group [6]; the recognized pediatric suicidality signal associated with antidepressants as a class [24,30] is the reason independent oversight with stop authority has been put in place.

Adverse Events and Safety Reporting

Adverse events are collected through participant report and investigator inquiry at every visit and are graded for severity and for relatedness to the investigational device using the 4-level scheme described above. SAEs are defined per the NMPA's medical device clinical trial regulations and include death, life-threatening events, permanent impairment of body structure or function, events requiring or prolonging hospitalization, events requiring intervention to prevent permanent impairment, and fetal distress, fetal death, or congenital abnormality. The investigator is required to report SAEs to the sponsor, the site clinical-trial administration office, and the ethics committee within 24 hours of awareness, with follow-up reporting at protocol-specified intervals. The sponsor is required to report device-related SAEs that result in death or life-threatening outcomes to the relevant provincial drug regulatory authority

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and to all participating centers within 7 calendar days of awareness, and other device-related SAEs and material safety information within 15 calendar days. Device defects are reported through a parallel channel within the same time windows.

Data Management and Quality Control

Data are captured in an EDC system using eCRFs. Role-based access controls separate the privileges of data-entry personnel, investigators, the principal investigator (who carries electronic-signature authority), monitors (clinical research associates), and data managers. Data queries are issued automatically by system rules and manually by monitors and data managers; query resolution, modification history, and electronic signatures are stored in an audit trail. After source-data verification by the monitor, query closure by data management, and electronic sign-off by the principal investigator, the database is locked, and the analysis dataset is exported.

Pretrial training covers protocol requirements, the rating-scale administration manual (with a CDRS-R interrater reliability check before site activation), eCRF completion, and device-management procedures. Monitoring is risk-adapted: the site visit frequency is set in proportion to enrollment rate and to site-level data quality. Source documentation is retained for 10 years after trial completion or termination at the participating site and at the ethics committee, in accordance with the applicable Chinese regulations.

Independently of routine sponsor monitoring, the sponsor may commission qualified auditors to evaluate site-level conformity with the protocol, the Chinese Good Clinical Practice standard, and applicable regulatory requirements. The participating sites and investigators are also required to permit on-site inspection by the NMPA and the relevant provincial drug regulatory and health administration authorities. The investigators and the coordinating center will cooperate fully with sponsor audits and regulatory inspections.

Posttrial Care and Compensation

The investigational software is withdrawn at trial exit, with device-usage rights returned to the sponsor as specified in the protocol's device-management procedures. Onward clinical care for participants whose depression has not fully remitted at the week-8 end point is provided through the standing services of the participating site, in accordance with the treating clinician's judgment and the Chinese Guidelines for the Prevention and Treatment of Depressive Disorders [6]. Should a participant sustain trial-related injury, the sponsor is responsible for the corresponding medical costs and for compensation in accordance with the applicable Chinese regulations on medical device clinical research; this responsibility does not extend to harms attributable to underlying disease progression or to investigator or site negligence.

Confidentiality, Data Sharing, and Dissemination

Participant identifiers are stored separately from research data, and only deidentified data are shared with the sponsor and used in analysis. Source records remain at the trial site and are made available for monitoring, audit, and regulatory inspection in accordance with the participant- and guardian-signed informed consent. Trial findings will be disseminated through publication in the peer-reviewed literature and through scientific-conference presentations; participant identity will not be disclosed in any publication. The sponsor has committed to release deidentified individual participant data on the RESMAN platform [31] during the window June 2029 to December 2029, in accordance with the registry undertaking.

Results

This section reports trial status as of July 30, 2026. The trial opened to enrollment on March 16, 2026, and is ongoing; the registry-recorded recruitment status is "Recruiting." The recruitment window extends to December 31, 2026. The last enrolled participant's 8-week visit will fall in the first quarter of 2027, and the registered final follow-up date of August 31, 2027, reserves the intervening months for late safety follow-up, source-data verification, query resolution, and database lock. The primary efficacy analysis is anticipated within the calendar year following the close of follow-up, with the primary results manuscript planned in parallel. Deidentified individual participant data and the locked statistical analysis plan will be released on the RESMAN platform during the registered window of June 2029 to December 2029.

Site-level enrollment counts and the completed CONSORT flow diagram will be reported in the results manuscript. No interim or planned analyses have been performed at the time of writing.

Discussion

Principal Results

This protocol describes a regulatory-grade evaluation of a smartphone-delivered, prescription-supervised CBT-based digital therapeutic for children and adolescents with current MDD, conducted in mainland China and embedded within a guideline-concordant pharmacotherapy framework. The trial addresses 3 persistent gaps in the pediatric digital therapeutics literature: a structurally matched, blinded comparator that controls for nonspecific digital engagement effects [15]; multicenter recruitment from tertiary-care hospitals with specialist psychiatric services, which improves the external validity of the findings beyond what a single-site sample can support; and the explicit integration of guideline-recommended pharmacotherapy in moderate to severe presentations, which aligns the experimental contrast with guideline-concordant care rather than with an idealized monotherapy comparison.

Limitations

Several design choices warrant explicit acknowledgment. The choice of a placebo-software comparator rather than treatment-as-usual or waitlist control is consistent with the cited regulatory guidance and with the precedent in the adolescent iCBT literature, but partially limits the inference about effectiveness relative to in-person CBT or to specialist treatment-as-usual; head-to-head comparisons against an active psychotherapy comparator are reserved for a subsequent study. The 8-week primary end point is shorter than the durations

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evaluated in some recent meta-analyses of iCBT in adults [7,8], which reflects the regulatory focus of the current trial on acute-phase efficacy rather than on relapse prevention; longer-term durability of effect will require extended follow-up in a future study. The exclusion of participants with prominent suicidal ideation (CDRS-R item 13 score above 4) is appropriate for a digitally delivered first evaluation in this age group, but means that the highest-risk pediatric patients are not represented in the inferential population. The CDRS-R entry threshold of greater than 30 is permissive relative to many adolescent depression trials, which often use a higher cutoff; this choice maximizes representativeness across the mild and moderate to severe presentations described by the Chinese guideline but means the inferential population includes participants whose baseline severity is below the moderate range. The asymmetric week-8 visit window (+7 days, with no negative tolerance) preserves the prospectively defined exposure duration but may modestly reduce the rate of complete primary-end point capture; the LOCF and MMRM sensitivity analyses are intended to address this.

Several further considerations are recognized. The prespecified primary missing-data approach is LOCF, in line with the protocol's V1.1 specification and the longstanding NMPA medical-device convention; International Council for Harmonisation E9(R1) increasingly recommends multiple imputation or reference-based imputation as preferred contemporary alternatives, and the MMRM sensitivity analysis already prespecified provides a check on the LOCF result. Suicide risk is assessed through CDRS-R item 13 combined with psychiatrist clinical judgment at every visit rather than through a structured instrument such as the Columbia-Suicide Severity Rating Scale, and clinical rescue is triggered by clinical judgment rather than a predefined numerical worsening threshold; both choices reflect the reality that all 7 visits are psychiatrist-conducted, but they reduce the standardization of risk ascertainment across sites. Treatment credibility and expectancy are controlled by the visually and structurally matched placebo and by blinding rather than measured with a credibility or expectancy questionnaire, so the success of blinding cannot be quantified directly; engagement, by contrast, is captured objectively through back-end stage-completion logging. Randomization is unstratified, with confounding by baseline severity, fluoxetine exposure, and site addressed through covariate adjustment rather than allocation, a choice dictated by the trial already being in progress when these specifications were strengthened. The absence of prespecified subgroup analyses by baseline severity, age band, sex, and site remains a limitation of the inferential plan.

Factors beyond efficacy will determine whether the intervention can be implemented at scale, and several are not resolved by this trial. Dashboard supervision imposes an additional and recurring demand on clinician time that this efficacy trial, conducted in well-resourced academic centers with dedicated study coordinators, is not designed to quantify; the workload implications for routine services remain unknown. Sustained engagement outside a trial context, where scheduled visits and research contact reinforce adherence, is likely to be lower than that observed here. Durability is untested: the 8-week end point characterizes acute-phase response, not maintenance of benefit or relapse prevention. Access is contingent on smartphone ownership, adequate data connectivity, and digital literacy in both the adolescent and the supervising guardian, and eligibility explicitly requires proficiency in smartphone use, so participants without these resources are not represented. Socioeconomic and geographic disparities in access to both smartphones and specialist prescribing clinicians may therefore limit equitable implementation, particularly outside major urban centers.

Generalizability is correspondingly bounded. Recruitment from tertiary-A hospitals with specialist psychiatric services selects a population with greater symptom severity, higher comorbidity screening, and better access to specialist care than the broader population of Chinese children and adolescents with depression; participants presenting to primary care, school health services, or community settings are not represented. The exclusion of prominent suicidality and of concurrent psychiatric disorders further narrows the inferential population relative to routine clinical caseloads, in which comorbidity is common. Claims about performance in routine practice should therefore be read as applying to supervised use within specialist pediatric psychiatric services rather than to unselected community care. Before wider implementation, pragmatic effectiveness trials in primary-care and school settings, trials permitting common psychiatric comorbidity, extended follow-up to assess durability and relapse, and head-to-head comparison with in-person CBT and IPT-A [14,32] will be needed.

Conclusions

The findings of this trial will inform the regulatory pathway for the investigational device in China and, more broadly, will contribute what is, to the authors' knowledge, among the first registration-grade randomized evidence on a smartphone-delivered DTx for pediatric MDD in a Chinese population. Should the superiority hypothesis be confirmed, the findings would support efficacy under supervised use in specialist pediatric psychiatric settings; establishing effectiveness in routine and community care would require the pragmatic studies outlined above. Future work will examine effect durability beyond the 8-week end point, comparative effectiveness against in-person CBT and IPT-A, and equity of access across socioeconomic and geographic strata.

Funding

Industry-sponsored: Beijing Wangli Medical Technology Co., Ltd. This work was additionally supported by the Beijing Municipal Science and Technology Commission (No. Z241100007724007) and the Beijing Nova Program. The industry sponsor was responsible for the design of the investigational device, contributed to protocol development, and is responsible for funding the conduct of the trial. The sponsor has no role in primary data collection at the participating sites, in the conduct of the primary

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statistical analysis, or in the editorial decisions regarding the publication of results. The coordinating center retains the contractual right to publish the trial findings independent of the sponsor's preference.

Data Availability

Deidentified individual participant data will be deposited on the RESMAN platform [31] during the window June 2029 to December 2029, accompanied by the analysis-ready data dictionary and the locked statistical analysis plan, in accordance with the registry undertaking.

Generative AI Use

The authors used a generative AI assistant to support language editing, formatting, and reference management during manuscript preparation. Generative AI was not used to generate study data, to design the trial, to conduct the statistical analyses, or to produce scientific conclusions. All content, including every factual claim, statistic, and citation, was reviewed, verified, and approved by the authors, who take full responsibility for the integrity and accuracy of the manuscript.

Authors' Contributions

Author contributions are reported following the CRediT taxonomy. JL (coordinating investigator): conceptualization, methodology, supervision, project administration, funding acquisition, and writing—review and editing. XL: conceptualization, methodology, investigation, project administration, and writing—original draft. QC: methodology, formal analysis, and writing—review and editing. LS and YQ: investigation, data curation, and writing—review and editing. MG and XW (site investigators): investigation, resources, and writing—review and editing. LW, WL, HW, and XH: investigation and data curation. The coordinating investigator is responsible for the integrity of the trial and for compliance with the protocol at the lead site. Authorship follows the International Committee of Medical Journal Editors (ICMJE) criteria, and no professional medical writers were engaged. All authors read and approved the final manuscript and agree to be accountable for the accuracy and integrity of the work.

Conflicts of Interest

The investigational device is registered to and sponsored by Beijing Wangli Medical Technology Co, Ltd (the industry sponsor of this trial) and is manufactured under contract by Sichuan Wangli Medical Technology Co, Ltd, a related corporate entity; these relationships are disclosed in the interest of transparency. Beyond this trial-level sponsorship, the authors declare that they have no personal financial or nonfinancial competing interests.

Multimedia Appendix 1

Informed consent and assent forms (English translation).
[PDF File (Adobe PDF File), 9529 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Sample-size sensitivity analysis.
[PDF File (Adobe PDF File), 1390 KB-Multimedia Appendix 2]

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Abbreviations

CBT: cognitive behavioral therapy
CDI: Children's Depression Inventory
CDRS-R: Children's Depression Rating Scale-Revised
CGI-I: Clinical Global Impression-Improvement
CGI-S: Clinical Global Impression-Severity
CONSORT: Consolidated Standards of Reporting Trials
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
DTx: digital therapeutics
eCRF: electronic case report form
EDC: electronic data capture
FAS: full analysis set
iCBT: internet-based cognitive behavioral therapy
IPT-A: interpersonal psychotherapy adapted for adolescents
K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version
LOCF: last observation carried forward
MDD: major depressive disorder
MMRM: mixed model for repeated measures
NMPA: National Medical Products Administration
PHQ-9: 9-item Patient Health Questionnaire
PPS: per-protocol set
PSQ: Conners' Parent Symptom Questionnaire
SAE: serious adverse event
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TIDieR: Template for Intervention Description and Replication

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