Integrated system of digital therapy and clinician care for perinatal depression and anxiety: a randomized controlled trial

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Research In Context

Evidence Before this Study. Evidence suggests that there are effective treatments for perinatal depression (PND), but barriers to care remain a persistent concern. Specifically, systematic reviews and meta-analyses indicate the efficacy of psychological therapies including cognitive behavioral therapies and interpersonal psychotherapy, and selective serotonin reuptake inhibitors. However, it is estimated that only 13-16% of women receive care for perinatal depression. In a meta-review, Webb and colleagues (2021) found that systemic factors were significant barriers to care. Digital or online therapies can increase access to care, and evidence suggests they are moderately effective for perinatal anxiety and depression. However, national treatment guidelines recommend digital therapies for only mild to moderate depression and recommend higher intensity clinical care for more severe depression. A system that combines accessible digital therapies for lesser depression severity and clinical care for greater depression severity is needed.

Added Value of this Study. This study evaluates the efficacy of a system of care that could increase access to evidence-based treatment for perinatal depression, and by so doing, address the significant public health burden and unmet need for treatment of perinatal depression in an innovative and novel way. This study compares the efficacy of a tiered system (in which women with moderately severe perinatal depression are triaged to digital therapy with coaching and women with severe depression are triaged to individual cognitive behavioral therapy with the option for pharmacotherapy) to reproductive-specialist psychiatric care. This study demonstrated equivalence between the two interventions on the primary outcome of depression, as well as secondary outcomes, indicating that the tiered system is a promising option that could increase access to care for this disabling public health condition.

Implications. This study provides an efficacious model of care based on existing best practices to specialist psychiatric care services for perinatal depression that has the potential to increase access to care by allocating resource-intensive clinical care to those who need it most while providing digital therapy with coaching to those with less severe symptoms. This approach could reduce the burden of perinatal depression.

Abstract

Background: Perinatal depression (PND) is prevalent and associated with impairment and multigenerational consequences. Effective treatments exist but are often challenging to access. This trial assessed the efficacy of a novel, tiered system of care for treating PND relative to perinatal psychiatric care. **Methods:** In this efficacy trial, women between 28 weeks pregnant and 6-months postpartum who scored ≥ 11 on the EPDS were recruited from an obstetrics clinic and randomized to (a) a tiered system called Screening and Treatment for Anxiety and Depression (STAND) that included digital cognitive behavioral therapy (CBT) with coaching for moderately depressed women, and CBT delivered by psychology doctoral trainees, with pharmacotherapy as needed delivered by psychiatry residents, for severely depressed or suicidal women; or (b) perinatal psychiatric care (PPC) involving supportive therapy, pharmacotherapy if needed, and community referrals, delivered by a psychiatry residents, regardless of depression severity. Participants were assessed for depression (primary), anxiety (secondary), and functional impairment (secondary) from baseline through 26 weeks follow-up. **Outcomes:** The sample was $N = 166$; $n_{PPC} = 88$ [53%], $n_{STAND} = 78$ [47%]. In STAND, 50 (76%) women received digital CBT with coaching, while 16 (24%) received face-to-face CBT and only 11% received pharmacotherapy. In PPC, 56 (76%) women received pharmacotherapy. The primary outcome was depression severity (via computerized adaptive testing), which significantly decreased over time (β =-0.05, 95% CI[-0.05, -0.04], $p < .0001$), with no differences between treatments (Condition: β =0.06, 95% CI[-0.20, 0.32], $p = .65$; Time x Condition: $\beta = 0.004$, 95% CI[-0.004, 0.01], $p = .38$), and with equivalence bounds as low as (-1, 1) (all ps < .0001). There was one serious adverse event in PPC, unrelated to treatment. **Interpretation:** A tiered system of care in which three quarters received digital CBT with coach support without pharmacotherapy was as

efficacious for PND as psychiatric care in which three quarters received pharmacotherapy. The STAND tiered system can increase access to care for PND.

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Trial Registration in NCT: 9/24/2021

NCT direct link:

https://www.clinicaltrials.gov/study/NCT05056454?term=NCT05056454&rank=1&a=1

Perinatal (antenatal and postnatal) depression (PND) is prevalent and associated with poor medical and mental health outcomes including self-harm, suicide, pre-term delivery, low birthweight, substance use and pre-eclampsia(1, 2). PND accounts for $14.2 billion annually in productivity losses and maternal health expenditures in the United States(3). Moreover, children of depressed mothers are at increased risk for internalizing and externalizing disorders, poorer cognitive development(4) and poorer academic performance(5).

Psychological and pharmacological treatment options exist for PND. Meta-analytic findings show that psychological treatments are effective and that cognitive behavioral therapy (CBT) and interpersonal therapy are superior to control conditions(6). Women also prefer psychological over pharmacological therapies(7). Systematic reviews indicate efficacy of selective serotonin reuptake inhibitors (SSRIs) for PND compared to placebo(6). Unfortunately, women who could benefit from these interventions rarely receive them, with estimates of only 13-16% of women receiving care for PND(8). Barriers include lack of availability of preferred psychological treatments, shortages of providers trained in perinatal mental health, systemic limitations in healthcare coverage, and unequal access to care(9). The perinatal period also presents unique challenges for attending therapy appointments (e.g., childcare demands, sleep deprivation, treatment burden). This may explain low utilization rates (e.g., 15-40%)(8, 10), especially for Hispanic and Black mothers(11), consistent with systemic issues of access to care being particularly pronounced for minoritized groups.

Digital or online therapies increase access to care(12) and are moderately effective for anxiety and depression in perinatal samples(13, 14). Although severity of depression is not a moderator of effects between digital vs face-to-face CBT(15), there are no published reports comparing digital CBT alone to face-to-face CBT with medication for severely depressed and

actively suicidal individuals. Treatment guidelines, such as those from the National Institute for Health and Care Excellence (NICE)(16), recommend digital therapies (and other lower intensity treatments) for mild to moderate depression and higher intensity clinical care for more severe depression. Following these principles, the Screening and Treatment for Anxiety and Depression (STAND) system of care triages individuals to self- or coach-guided digital CBT, or to clinician-delivered CBT with pharmacological treatment as needed, depending on symptom severity. In this way, costly clinical resources are reserved for those with the most acute need. A notable feature of STAND is that symptoms are continuously monitored, and level of care is rapidly adapted as needs change over time. For example, indication of reliable symptom worsening for those receiving digital CBT triggers shifting to clinical care. The STAND model has been previously tested in college student samples, with evidence for substantial and significant improvement in anxiety, depression and suicidality in an open trial(17).

The present study evaluated the efficacy of a version of STAND tailored to PND in comparison to perinatal psychiatric treatment (PPC) consisting of supportive therapy with pharmacotherapy and community referrals. This efficacy study balanced internal and external validity and included some implementation-related outcomes related to clinical outcome (e.g., treatment utilization/engagement). It was hypothesized that STAND would be superior to PPC on primary measures of depression and secondary measures of anxiety and functioning.

Method

Trial Design

This was an assessor-blinded, randomized (1:1), two-arm, clinical superiority trial for PND conducted in the greater Los Angeles area. The Institutional Review Board (IRB-20-1924) at the University of California – Los Angeles (UCLA) reviewed and approved all study

procedures, and all participants signed consent. The trial was pre-registered (ClinicalTrials NCT05056454) and the study protocol was published(18).

Participants

Participants were between week 28 of pregnancy and 6 months postpartum at the time of recruitment, receiving care at UCLA OB-GYN clinics, 18 years and older, fluent in English, had internet access, and scored ≥ 11 on the 9-item Edinburgh Postnatal Depression Scale (EPDS)(19) [1]. Exclusion criteria were (a) already undergoing treatment for anxiety, depression, or related conditions; or (b) diagnoses that required a higher level of care (e.g., Intensive Outpatient Program) or specialty care (e.g., substance use disorder specialty care), such as recent suicide attempts, non-stabilized bipolar disorder, psychotic disorder, severe substance use disorder (see Supplemental materials). These diagnoses were determined using the Series of Assessments for Guiding Evaluation-Self-Report (SAGE-SR) (see Measures, below). All study procedures were reviewed and approved by UCLA Institutional Review Board. The study protocol is published(18).

Randomization and masking

Participants were randomized to STAND or PPC via computer-generated random allocation, without stratification. Random assignments were made 1:1 STAND to PPC in blocks of 6 from a randomization list that was held separately from the database. Random assignment was automatically imported to each record in the database after consent. Staff who ran the database function to import the random assignment did not have access to the list of assignments. Participants were not informed of their treatment condition until after completing the baseline

[1] Psychometrics and cut-offs for severity of depression do not differ between the full, 10-item version and the 9-item version of the EPDS from which the item that measures thoughts about self-harm is removed (Qiu et al., 2023). A range of elevated EPDS scores has been shown to identify depression (e.g., 10-14; O'Connor et al., 2016; Qiu et al., 2023), though a cut-off score of 11 or higher was found to be optimal to meet both DSM-5 and ICD-10 criteria for depression (Smith-Nielsen et al., 2018). Therefore, EPDS scores of 11 or greater were required to be eligible for the current study.

assessment. Study coordinators enrolled and assigned participants to care according to the randomization. Neither patients nor treatment providers could be blinded due to the nature of the interventions, and there were no assessors in this study, as all assessments were conducted online.

Measures

Diagnostic Assessment

The SAGE-SR is a brief, structured self-report of diagnostic criteria, compatible with ICD-10 and DSM-5(21). It has good to excellent test-retest reliability(21), and, while not validated against the SCID, has been utilized in perinatal samples(22). The SAGE-SR was administered at baseline for provisional diagnostic and exclusionary purposes.

Mental Health Outcomes

Computerized Adaptive Testing for Mental Health (CAT-MH): Depression and Anxiety Severity. The CAT-MH provides brief, adaptive tests of various mental health dimensions: depression and anxiety symptom severity were assessed herein. These scales are reliable and valid(23), including in perinatal women(24). In PPC, the CAT-MH was administered every other week from baseline through week 26, to provide high frequency outcome measurement, but the scores did not inform measurement-based care. In STAND, the CAT-MH was administered weekly and informed measurement-based care. CAT-MH Depression symptom severity was the primary outcome and CAT-MH anxiety symptom severity was a secondary outcome (neither is a diagnostic scale). On both scales, scores of 0-35 are considered the normal range, 35.1-65 are mild, 65.1-75 are moderate, and 75.1-100 are severe. The CAT-MH measures depression (and anxiety) on a 100-point scale within 5 points of precision: change of more than 5 points is meaningful.

Choice of primary measure. The CAT-MH was selected as the primary outcome given its reliability and validity(23, 25), including in perinatal women(24), plus brevity and lesser vulnerability to responder bias over high frequency repeated assessments relative to standardized scales. CAT-MH scores correlate highly with PHQ-9 and EPDS scales in perinatal samples (24). Access to the CAT-MH is obtained through a paid license from Adaptive Testing Technologies, based in Chicago, IL. It can be implemented via the vendor's user portal or API integration. The assessments are available in English and Spanish. Further details on CAT-MH development are in Supplemental Materials.

Edinburgh Postnatal Depression Scale (EPDS). The 9-item EPDS (suicidality item excluded) performs similarly to the full EPDS(20) that is both validated and reliable(26) and was a secondary outcome measure to assess depression. The EPDS is a widely used, validated screening tool specifically designed for use with women during the perinatal period. It was administered at baseline, week 13, and week 26. EPDS items are scored from 0 to 3, with higher scores indicating more severe depression. Reliability for this measure at baseline was acceptable ($\alpha = 0.78$).

Sheehan Disability Scale (SDS). Functional impairment in family, work, and social domains was assessed using the 3-item Sheehan Disability Scale(27) as a secondary outcome. The SDS is a widely-used measure of disability and has been used to assess disability in perinatal populations(28). The SDS has high internal consistency and construct validity(29). It was administered at baseline, week 13, and week 26. SDS items are scored from 0 to 10, with higher scores indicating higher functional impairment. Reliability for this measure at baseline was good ($\alpha = 0.83$).

Credibility, Expectancy, and Feedback

To ensure that there were no differences between conditions on the perceived credibility of their assigned treatment, treatment credibility and expectancy were assessed 4 weeks after baseline and at post-treatment using the 5-item Credibility/Expectancy Questionnaire (CEQ)(30), which has excellent internal consistency(30). Given the impact of expectancies on engagement and treatment outcomes, this is a standard approach to ensuring that outcomes are not biased by one condition being considered more credible than the other, particularly when evaluating the efficacy of a novel intervention approach such as STAND.

Adverse events

Adverse events were defined as suicidal intention (recorded via contact with coaches or clinicians, or weekly suicide severity scales within STAND) or worsening and severe depression from baseline to week 26 (recorded via CAT-MH depression). Serious adverse events were defined as death, suicide attempt, self-harm, or referral to crisis care or admission to inpatient care for suicidality or drug use (recorded via contact with coaches or clinicians).

Procedure

Recruitment occurred from August 2021 - October 2023. Follow-up assessments continued through March 2024. Participants were referred by UCLA obstetricians and reproductive psychiatrists, facilitated by review of medical records by study staff. Potential participants were phone contacted for screening. Participants were randomized to either STAND or perinatal psychiatric care (PPC). All clinical services in both conditions were provided through the UCLA Depression Grand Challenge (DGC) Clinic, a research clinic focused on delivering and evaluating the efficacy and effectiveness of STAND for various populations. Treatment and research assessments were all conducted completely remotely via the internet.

Interventions

See Table 2 for summary of the two intervention conditions, and Supplement Figure 1 for a depiction of the STAND model of care.

1. Screening and Treatment of Anxiety and Depression (STAND)

Following a stratified approach(31), women assigned to STAND were triaged into one of two levels of care based on presenting symptom severity. Women with CAT-MH depression scores ≤ 75 and no current suicidality were triaged to digital CBT tailored to PND with coaching. Those with severe depression scores (≥ 75.1) or above threshold on the CAT-MH suicidality scale were triaged to clinical care. See Supplemental materials and previous articles(17, 18) for details.

i. Ongoing Assessment/Measurement-based Care. Participants in STAND completed CAT-MH assessments weekly throughout the 6-month study to inform adaptations to care.

ii. Adaptation of Care. Participants triaged to digital CBT with coaching could be switched to clinical care if depression worsened or if suicidality thresholds were met. Continued weekly CAT-MH assessments could instigate re-initiation of treatment after initial treatment completion.

iii. Suicide Risk Management. Outreach and follow-up by the clinical team and a third-party service was triggered by above-threshold CAT-MH suicidality scores, completed weekly.

iv. Digital CBT with Coaching (for moderately severe depression). A change in access to digital programs mid-stream led to two versions of digital CBT, each with evidence from prior RCTs. The first set of participants received a link to a 3-module digital CBT program for perinatal depression and anxiety(13, 32) with six optional modules for anxiety and depression(33), created by THIS WAY UP (TWU)(13), a non-profit entity that provides digital

CBT for anxiety and depression[2]. Each module included homework exercises. The second set of participants received an updated version of a digital CBT program shown to be effective for PND(34), that was fully integrated into the DGC STAND platform. This program (DGC PND digital therapy) included five core lessons emphasizing behavioral activation, challenging negative thoughts, self-compassion and imagining positive autobiographical memories, and five optional lessons, each with homework. See Supplemental materials for details on the two digital programs.

For both versions of digital therapy, a coach answered questions about the digital materials and facilitated design of, and problem solved barriers to, home practice. Participants typically worked with the same coach over time. The maximum number of zoom coaching sessions matched the number of lessons (9 for TWU vs 10 for DGC PND digital therapy) over 10 weeks. See Supplement for information about the coaches and their training.

v. Clinical care (for severely depressed or actively suicidal). For those assigned to clinical care within STAND, clinical psychology doctoral students provided individual CBT via telehealth. In line with best practices in CBT, clinicians provided weekly therapy sessions, personalized to the needs of each participant, with number of sessions driven by measurement-based care using CAT-MH scores. Cognitive and behavioral strategies were selected by clinicians (under supervision) to match principal problem areas identified in a functional assessment. See Wolitzky-Taylor et al.(18) and the Supplement for details. Therapists received weekly supervision by licensed clinicians. Those assigned to STAND clinical care were provided pharmacotherapy administered by psychiatry residents when deemed appropriate during weekly case conferences attended by all providers and supervisors. Medication prescriptions followed

[2] An initial research agreement with TWU was for a pre-determined specified period of time; after that agreement ended, we switched to another digital therapy for PND created specifically for this study. The two digital therapies comprised very similar cognitive and behavioral therapy principles, skills, and exercises applied to perinatal depression.

best practices for perinatal populations, typically SSRIs considered safe during pregnancy and breastfeeding (e.g., sertraline(35)).

2. Perinatal Psychiatric Care (PPC)

All women randomized to PPC (regardless of depression severity) were treated by psychiatrists who provided a comprehensive diagnostic assessment, standardized supportive therapy, shown to be effective for depression, and pharmacotherapy(36) following best practices for perinatal populations (see above)(35). Psychiatry residents were supervised by a reproductive psychiatrist. Medication options were discussed and the most typical medication prescribed was sertraline, given its safety and efficacy in perinatal populations. Psychiatrists were instructed not to deliver any specific cognitive, behavioral, or other active treatment strategies but to provide supportive therapy (e.g., active listening, empathic statements). The protocol involved an initial intake evaluation followed by up to 3 sessions of supportive therapy and medication management, with the goal of transferring care to an outside provider (e.g., primary care provider, OBGYN, or psychiatrist practicing outside of the study) once medication dosage was stabilized. Community referrals for longer-term care were provided at the final visit to a psychiatrist, therapist, or primary care provider. CAT-MH was collected bi-weekly in the PPC condition but did not inform measurement-based care. See Supplement for more details.

Data Analysis Plan

Power Analysis. Details of the power analysis can be found in the Supplement. In brief, power for the comparison between PPC and STAND was based on published effect sizes for the effect of CBT on perinatal depression symptoms.[16] Based on these estimates, we expected to have sufficient power to detect depressive symptom differences previously reported in the literature in a sample of 120 women. When a new digital CBT program was introduced into the STAND condition (at enrollment $n = 94$), we generated a secondary aim of evaluating

equivalence between the two digital CBT programs within STAND. A power analysis using an effect size estimated from the participants who were assigned to TWU digital CBT in the first set of participants (n = 30) was conducted to determine the sample size needed for the second set of participants. Analyses demonstrated that we could show equivalence for bound values above (-5,5) on the CAT-MH for sample sizes > 20 and all standard errors explored(37). To be sufficiently powered to compare the two digital CBT versions, while taking into account expected 75% allocation to digital CBT + coaching within STAND and 25% attrition, 72 new randomizations were added (36 per condition), for a total N = 166.

Although the pre-specified analytic plan was to evaluate superiority of STAND vs PPC, we also completed a power analysis to demonstrate that our study maintained adequate statistical power to detect equivalence between treatment conditions. We used two-one-sided tests (TOST) to assess our power to demonstrate treatment equivalence using clinically meaningful equivalence bounds based on prior literature: (-1,1) to (-5,5) for CAT-MH depression and CAT-MH anxiety, since a value of 5 points is considered to be meaningful within an individual[13,14]; (-1,1) to (-4,4) for EPDS(38) and for SDS(39) since change scores of ≥ 4 represent clinically significant change. Across all tested equivalence bounds, our study achieved very high statistical power (approaching 1.0) to detect equivalence between treatment conditions.

Analytic Approach. Primary analyses to compare STAND to PPC used intention-to-treat linear mixed models, with participants at Level 2 and repeated measurements (i.e., different time points) at Level 1. Although the protocol specified adjusting for baseline values as covariates, the final analysis used longitudinal mixed-effects models in which baseline was included as the first observation in the repeated outcome. This approach estimates change over time within a single model and uses maximum likelihood to incorporate all available repeated observations. Linear mixed effect models were implemented in RStudio (Version 2024.04.2+764) (Posit Team,

2024(40)) using the lmer function from the 'lme4' package. Mixed-effects models were estimated using maximum likelihood estimation. Participants were included if they had at least one observed outcome measure. Longitudinal mixed-effects models were estimated using maximum likelihood, which incorporates all available observations without imputing missing values; therefore, participants with incomplete data across timepoints were retained. Although we applied intent-to-treat principles by retaining the full randomized sample (N = 166) in our models, estimation was based only on participants with available outcome and covariate data (n = 145) (15 participants did not complete any assessments, and 6 additional participants were missing covariates). To evaluate potential attrition bias, participants with and without post-baseline data were compared on baseline demographic and clinical variables using independent samples *t*-tests and χ^2 tests. See Supplemental Table S1 for available data at each measurement time point for each outcome variable.

Time was modeled from baseline through week 26, with 13 (biweekly, PPC) or 26 (weekly, STAND) assessments for CAT-MH depression and anxiety severity and was modeled for 3 assessments separated by 13 weeks for EPDS and SDS. The linear effect of time was centered to treatment condition differences at 26 weeks.

Four models were examined: CAT-MH depression severity (primary outcome), CAT-MH anxiety severity, EPDS depression, and SDS functional impairment. The baseline value of the dependent variable was treated as part of the repeated measures outcome as this approach (1) preserves within-individual correlation structure, (2) avoids regression-to-the-mean bias, and (3) maximizes statistical power. Condition (PPC coded 0, STAND coded 1; Level 2), Time (Level 1), Time x Condition interaction, and digital therapy (i.e., two versions of digital CBT; 0 = TWU, 1 = DGC PND digital therapy) were modelled as fixed effects with a random intercept for

participant. Gestational age (Level 2) was included as a covariate because it reflects postpartum timing at study entry and measurement timing, which is clinically and methodologically relevant to symptom trajectories independent of randomization. Sensitivity analyses were conducted for protocol violations ("protocol deviation analyses"): specifically comparing STAND participants to PPC participants with ≤ 4 psychiatry visits (per protocol).

Secondary analyses of equivalence were conducted using RStudio 2023.03.0+386(40) using the 'TOSTER' package(41). We used the standardized effects of time for each version of digital therapy/each treatment condition and ranged the equivalence bound from point difference in outcomes. Equivalence bounds were determined based on a difference that would be considered clinically equivalent (see above). A change of more than 5 points for CAT-MH and more than 4 points for both the EPDS and SDS are considered clinically meaningful. Thus, any between-group differences within those ranges are considered equivalent. The level of statistical significance for all analyses was $p < .050$. See Supplemental materials for further detail on power analyses for tests of superiority and equivalence.

Post-hoc analyses examined clinically significant change. On the CAT-MH, this metric was operationalized as 1) reliable change (using the reliable change index(25, 42)), as indicated by a reduction of at least 15.74 (depression) or 17.10 (anxiety) points, and 2) scoring 65 or less (representing mild or lesser severity). See Supplemental materials for details. For the EPDS, we calculated the percent who achieved week 26 remission according to EPDS < 10. These indices were calculated for participants with data available at Week 26 (n = 87 for CAT-MH, n = 91 for EPDS). χ^2 and risk ratio tests were performed to examine potential meaningful difference in outcome likelihood between groups.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report or decision to submit the report for publication.

Results

Analysis Populations

After enrolling 94 participants, a new digital CBT program was introduced into the STAND condition. With the addition of 72 participants to the initial cohort of 94 participants, our final sample size for the primary analysis comparing STAND to PPC was $N = 166$.

Missing Data & Study Attrition

Rates of missingness for CAT-MH (weekly/biweekly) were 62% for STAND and 70% for PPC. Rates of missingness for EPDS and SDS (baseline, week 13 and week 26) were 36% for STAND and 28% for PPC.

Bivariate comparisons revealed no significant differences between participants who completed an assessment after baseline vs. those who completed only baseline with respect to baseline demographic or clinical characteristics (all *ps* > .050).

Participant and Group Characteristics

As shown in the CONSORT diagram (Figure 1), 408 potential participants were assessed for eligibility. 242 were excluded, resulting in 166 participants randomized. Due to missing data at baseline, 145 were included in the final analytic sample for mixed-effects models. Descriptive data are presented in Table 1.

Treatment Engagement/Utilization of Services

Within PPC, 74 (84%) initiated care (attended initial intake with psychiatrist), and of those, 56 (76%) received medication management, with a mean of 3.90 (*SD* = 1.47; Median = 4; interquartile range [IQR] = 2) visits with the psychiatrist (range = 1-8).[3]

Within STAND, 66 (85%) initiated care (i.e., attended orientation session with coach or clinician), and of those, 50 (76%) received digital CBT with coaching and 16 (24%) received clinical care. Three participants originally triaged to STAND digital CBT with coaching were provided with STAND clinical care due to increased severity of depression/suicidality. Women in STAND digital CBT with coaching had a mean of 5.36 (*SD* = 3.24; median = 5; IQR = 5) digital lessons and a mean of 6.84 (*SD* = 3.40; median = 8, IQR = 6) coaching sessions. Women in STAND clinical care received a mean of 9.31 (*SD* = 6.37; median = 9; IQR = 10.75) therapy visits and 5 (31%) received medication management (*M* = 1.19 [*SD* = 1.97] visits; median = 0; IQR = 2.25). Across the STAND condition (combining digital CBT + coaching and clinical care), only 7 (11%) participants who initiated care received medication management.

Primary Outcome Measure of Depressive Symptoms: CAT-MH Depression Symptom Severity

There was a significant main effect of Time (β = -0.05, 95% CI[-0.05, -0.04], $p < .0001$), indicating substantive reductions in depression symptom severity (Figure 2A). The effect of Condition was non-significant (β = 0.06, 95% CI[-0.20, 0.32], $p = .65$), indicating no significant group differences at Week 26. The Time x Condition interaction was non-significant (β = 0.004, 95% CI[-0.004, 0.01], $p = .38$). At the study endpoint, estimated marginal means of scaled depression severity were similar between conditions (PPC: *M* = 0.04, *SE* = 0.18, 95% CI[-0.31, 0.39]; STAND: *M* = 0.05, *SE* = 0.19, 95% CI[-0.33, 0.43]), with a mean difference of −0.01 (*SE*

[3] Participants' care was bridged until they were able to establish care with an outside provider. Although the protocol specified a psychiatric evaluation and up to three supportive therapy + medication management visits (totaling 4 sessions), outside providers were not always available resulting some patients remaining in the care of their PPC provider for more than the prescribed 4 sessions, thus representing a protocol deviation.

= 0.12, $t(151) = -0.08$, $p = 0.94$), adjusted for gestational age and digital therapy version. Secondary analyses of treatment equivalence demonstrated lack of meaningful differences (STAND Effect of Time: $\beta = -0.04$, $SE = 0.003$; PPC Effect of Time: $\beta = -0.05$, $SE = 0.003$), with bound values as low as (-1, 1) (all ps < .0001).

Post-hoc Analysis of Clinically Significant Change. Reliable CAT-MH depression severity reduction was achieved by 68% in PPC and 62.2% in STAND; the proportions did not significantly differ ($\chi^2(1) = 0.11$, $p = .74$; Risk Ratio [RR] = 1.18, 95% CI of RR [0.66-2.11]).

Secondary Outcome Measure of Depressive Symptoms: Edinburgh Postnatal Depression Scale

There was a significant main effect of Time ($\beta = -0.06$, 95% CI[-0.07, -0.05], $p < .0001$) (Figure 2B). The effect of Condition was non-significant ($\beta = 0.10$, 95% CI[-0.20, 0.40], $p = .52$), indicating no significant group differences at Week 26. The Time x Condition interaction was non-significant ($\beta = 0.01$, 95% CI[-0.01, 0.02], $p = .30$). At the study endpoint, estimated marginal means of scaled depression severity were similar between conditions (PPC: $M = 0.11$, $SE = 0.16$, 95% CI[-0.20, 0.42]; STAND: $M = 0.10$, $SE = 0.17$, 95% CI[-0.24, 0.43]), with a mean difference of 0.01 ($SE = 0.11$, $t(145) = 0.12$, $p = 0.90$), adjusted for gestational age and digital therapy version. Secondary analyses of treatment equivalence demonstrated lack of meaningful group differences (STAND Effect of Time: $\beta = -0.05$, $SE = 0.005$; PPC Effect of Time: $\beta = -0.06$, $SE = 0.005$), with bound values as low as (-1, 1) (all ps < .0001).

Post-hoc Analysis of Clinically Significant Change. An EPDS score < 10 was achieved for 71% in PPC and 69% in STAND. The proportions did not significantly differ ($\chi^2(1) < 0.001$, $p = 1.00$; RR = 1.07, 95% CI of RR [0.56, 2.01]).

Secondary Outcome: CAT-MH Anxiety Symptom Severity

There was a significant effect of Time (β = -0.05, 95% CI[-0.05, -0.04], p = .0001), indicating substantive reductions in anxiety severity. The effect of Condition was significant, indicating that anxiety severity was significantly lower in PPC than STAND at Week 26 (β = 0.30, 95% CI[0.03, 0.56], p = .028). Further, the Time x Condition interaction was significant (β = 0.01, 95% CI[0.005, 0.02], p = .0016) (Figure 2C), indicating a steeper slope of anxiety severity reduction for PPC than STAND. At the study endpoint, estimated marginal means of scaled anxiety severity were similar between conditions (PPC: M = 0.001, SE = 0.18, 95% CI[-0.36, 0.36]; STAND: M = 0.11, SE = 0.20, 95% CI[-0.27, 0.50]), with a mean difference of -0.11 (SE = 0.12, t(151) = -0.94, p = 0.35), adjusted for gestational age and digital therapy version. Secondary tests of treatment equivalence demonstrated lack of meaningful differences between STAND and PPC, (STAND, Time: β = -0.04, SE = 0.003; PPC, Time: β = -0.05, SE = 0.003), with bound values as low as (-1, 1) (all ps < .0001).

Post-hoc Analysis of Clinically Significant Change. Reliable CAT-MH anxiety severity reduction was achieved by 70% in PPC and 65% in STAND. The proportions did not significantly differ ($\chi^2(1) = 0.08$, p = .78; RR = 1.17, 95% CI of RR [0.64–2.15]).

Secondary Outcome: Sheehan Disability Scale

There was a significant main effect of Time (β = -0.04, 95% CI[-0.05, -0.03], p < .0001) (Figure 2D), indicating substantive improvements in functioning. The effect of Condition was non-significant (β = -0.17, 95% CI[-0.50, 0.17], p = .34), indicating no significant group differences at week 26. The Time x Condition interaction was non-significant (β = -0.004, 95% CI[-0.02, 0.01], p = .63). At the study endpoint, estimated marginal means of scaled disability severity were similar between conditions (PPC: M = 0.21, SE = 0.19, 95% CI[-0.16, 0.58]; STAND: M = 0.10, SE = 0.20, 95% CI[-0.30, 0.50]), with a mean difference of 0.11 (SE = 0.13,

$t(148) = 0.87$, $p = 0.38$), adjusted for gestational age and digital therapy version. Secondary tests of treatment equivalence demonstrated lack of meaningful differences between STAND and PPC, (STAND, Time: $\beta = -0.04$, $SE = 0.006$; PPC, Time: $\beta = -0.03$, $SE = 0.005$), with bound values as low as (-1, 1) (all ps < .0001).

Additional Analyses

Please see the Supplement for information about protocol deviation analyses, comparison of the two forms of digital therapy, and credibility and expectancy ratings between groups.

Adverse Events

There was one serious adverse event of unstable suicidality that resulted in crisis referral and eventual hospitalization; hospitalization (PPC condition) that was unrelated to study procedures. There were four incidents of patient-reported suicidal intention within STAND, but in no case did follow-up assessment warrant further action. Worsening of CAT-MH depression (increase of at least 7.29 points from baseline to follow-up and scoring ≥ 75.1, severe) occurred for 4 women (PPC, n=1 [2%]; STAND, n=3 [5%]).

Discussion

This study evaluated the efficacy of a novel, tiered approach to perinatal depression relative to perinatal psychiatric care. Three quarters of women who were randomized to STAND and initiated care received digital CBT tailored to the needs of perinatal mental health, supported by telehealth coaches who were bachelors' level and psychology doctoral students in training. Under one quarter received face-to-face (via telehealth) CBT from psychology doctoral students, and one in ten received pharmacotherapy. In contrast, all women randomized to PPC who initiated care were treated by a psychiatrist who provided supportive therapy, pharmacotherapy, and referrals to resources in the community.

Contrary to hypotheses, STAND did not show superior clinical outcomes compared to PPC. Instead, STAND was shown to be equivalent to PPC across primary and secondary measures of depression and functional impairment, all of which showed substantive improvements. PPC showed a steeper decline in anxiety and lower anxiety than STAND at the 26-week assessment, perhaps related to psychiatrists' allaying concerns regarding pregnancy, birth or infant care, although equivalence testing demonstrated no meaningful differences in the anxiety outcome between the two conditions. It is worth noting that PPC represented considerably more enhanced treatment than PND care in an average community-based OBGYN or primary care setting. As such, PPC represents a stringent, evidence-based comparison treatment, rather than a treatment-as-usual comparison in which patients would only receive what is available to them in their real-world setting. Indeed, the vast majority of women with perinatal depression do not receive care at all(8) and even screening alone is not standard practice(43). Moreover, PPC participants received, on average, more than the prescribed number of psychiatric visits (although results were unchanged when the sample was limited to those receiving the protocolized ≤ 4 visits). This was largely due to barriers in establishing care with outside providers and a need to bridge care until referrals were accomplished. The lack of community mental health resources and providers trained in perinatal mental health[14-16] is a major impetus for systems of care such as STAND. In hindsight, it makes sense that the PPC condition would be subjected to the very barriers to accessing care that the STAND system is addressing(8, 43). Although speculative, a possible explanation for lack of superiority of STAND over PPC is that it is those in STAND were non-adherent, or only modestly adherent to homework recommendations. Unfortunately, we did not assess CBT homework adherence. Given the

importance of home practice of CBT skills for optimizing clinical outcomes(44), the potential of STAND may have been mitigated due to homework non-adherence.

Women found digital CBT with coaching acceptable, and the high adherence rates (averaging five digital lessons) may be tied to coaching, which is linked with higher completion rates(12), especially for samples with moderate to severe symptoms(45), including perinatal populations(46). Digital therapies offer special advantages for women in late pregnancy or early child rearing, allowing time to complete therapy on their own schedule around needs of pregnancy and baby.

Women with severe depression were also highly engaged with STAND clinical therapy, averaging nine individual CBT sessions. Only one third (31%) of those assigned to clinical care within STAND received medication management, such that across both levels of STAND care, only one in ten women received medication for their depression. These findings add to the growing body of research demonstrating the efficacy of CBT as a first-line treatment for perinatal depression(47).

Overall, credibility and expectancies about STAND were high and trended towards being higher than in PPC. Also, rates of initiating care did not differ from those randomized to PPC, averaging 84%; these rates compare favorably to other treatment studies of perinatal depression(48). The results illustrate the value of an integrated model for care that is more accessible for women with perinatal depression and provide justification for future the study of cost effectiveness of STAND.

The study included controls to internal validity (e.g., randomization, expert clinical supervision and attention to clinical protocols) with an emphasis on real-world applicability (e.g., recruitment of patients from OBGYN clinics, flexibility within treatment). Although the study

was not conceptualized as an implementation trial, the comparison of a *system* of care that included many personalized elements, such that not all participants in the STAND condition received the exact same treatment, has direct implications for implementing much-needed systems of care in clinical settings. Moreover, the assessment of engagement in that system provides preliminary data to support a future implementation trial.

Despite the many strengths of this study, there are limitations worth noting. Persons with lived experience were not involved in the study design or methods development and should be included in future research. Also, we may not have been powered to detect small effects and effects on non-depression outcomes when comparing STAND to PPC. This is particularly important given that PPC was a highly stringent comparison group that went beyond treatment as usual. In light of the lack of between-group differences, it could be argued that improvements were not due to either STAND or PPC, but rather time alone or nonspecific treatment effects. On the other hand, a wealth of prior research demonstrates that both CBT and pharmacotherapy for perinatal depression show superior clinical outcomes compared to waitlist and other non-active control conditions(47, 49), indicating that the interventions included in the current study were efficacious and that improvement was not likely to be due simply to the passage of time.

Also, external validity is limited by the fact that the study was a single-site, university-affiliated clinic and that only English-speaking patients with internet access were included. Future research with community-based sites and more diverse samples are needed. Additionally, a substantial number of women were withdrawn from the study for reasons of nonresponsiveness, possibly related to the pregnancy, childbirth, infant care and other challenges during the perinatal period. Missing data is a ubiquitous problem in real-world clinical trial research, that may limit our ability to draw firm conclusions. Our statistical analyses accounted

for these missing data using highly acceptable approaches that give us confidence in our estimated outcomes, but research to evaluate whether these findings replicate is needed. Fourth, coaches were a mix of bachelors' level staff and clinical psychology doctoral students. Future research should evaluate whether level of training and experience impacts outcomes, since greater effects of behavioral treatment for PND have been observed when delivered by mental health and health providers compared to non-professional providers(14). We did not adequately track how much PPC participants utilized the outside resources to which they were referred, which may have impacted treatment outcomes. While the two versions of digital CBT have each been shown to be effective in prior RCTs, and the two versions showed equivalence, cohort effects may have existed. There were fewer severely depressed women than women with mild and moderate depression, so additional research is needed with more severe samples. Future research should evaluate replicability and generalizability beyond a university connected OB clinic and women willing to be randomized in a treatment trial. Other avenues for future investigation include cost effectiveness and patient preferences. Along these lines, future research should examine barriers to successful implementation in routine perinatal care settings. In particular, efforts to establish coaches within these systems and provide pathways for billing these services is critical to the sustainability of STAND following research.

Taken together, these findings indicate that a tiered and adaptive system of care that relies principally on digital CBT with telehealth coaching, with clinical care reserved for severely depressed women, is as efficacious for perinatal depression as perinatal psychiatric care, which included supportive therapy, medication management, and referrals to outside resources. Anxiety reduction, however, occurred more rapidly and to a greater extent by the end of the study for women who received perinatal psychiatric care. Nonetheless, the general equivalence

of clinically meaningful effects between STAND and perinatal psychiatric care on all measures, including anxiety, is especially significant given the concerns many women have with regards to psychotropic medication use during pregnancy and breastfeeding(50). The provision of a treatment model that does not rely on medication except in the minority of cases will be of great value for women and OB and other antenatal postnatal clinics. Future research that aims to both replicate these findings and examine the feasibility of implementation into larger-scale health systems, adding comprehensive implementation measures, is an important next step. Current and future directions aim to develop streamlined and scalable models of STAND to increase the likelihood and feasibility of implementation and sustainability. These include streamlining the training and supervision for coaches and clinicians, as well as exploring how workforces embedded in relevant clinical settings (e.g., OBGYN clinics) may work most effectively in coordination with psychology/psychiatry specialty care to increase access to this care.

Data Sharing Statement

De-identified data along with a data dictionary are available upon reasonable request. Individual participant data that underlie the results reported in this Article can be shared with researchers who provide a methodologically sound proposal to the corresponding author. Proposals can be submitted up to 36 months after publication of this Article.

Contributors: MGC, KWT, MCR designed the study and were responsible for its conduct. NF provided input on the design. MGC, KWT, MCR and SF contributed to the development of treatment manuals and supervision. JMN and MRM provided THISWAYUP digital therapy and HOM contributed to the development of the DGC PND digital therapy. AW, VMcD and IA were responsible for the collection and management of the study data. AM, MGC and KWT drafted the analysis plan and AM, BB, and FH conducted the statistical analyses. MGC, KWT, AM and NF interpreted the data. MGC, KWT, AM, and AW drafted the manuscript. All authors were involved in critically revising the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

Declaration of interests. We declare no competing interests.

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Table 1

Demographic and Baseline Clinical Characteristics of Participants in STAND and PPC

	STAND (n=78)		PPC (n=88)	
Age	**M/Count**	***SD/%***	**M/Count**	***SD/%***
Maternal age (Years)	33.97	5.68	32.69	5.46
Time of recruitment (pre or post birth)				
< 28 weeks gestation	0	0	1	1.1
Gestation 28-34 weeks	10	12.8	10	11.4
Gestation 35-44 weeks	11	14.1	8	9.1
Post-birth 0-6 months	47	60.3	56	63.6
> 6 months post-birth	0	0	2	2.3
Missing	10	12.8	11	12.5
Race				
American Indian/Alaskan Native	1	1%	0	0%
Asian/Asian-American	17	22%	11	13%
Black/African American	6	8%	5	6%
Native Hawaiian/other Pacific Islander	0	0%	0	0%
White/Caucasian	24	31%	41	47%
Multiracial (i.e., >1 race reported)	9	12%	7	8.0%
Other/Not Reported	21	27%	24	27%
Ethnicity				
Hispanic/Latino/a/x/e	26	33%	30	34%
Non-Hispanic/Latino/a/x/e	52	67%	58	66%
Marital Status				
Single; never married	7	9%	10	11%
Living w Partner/Domestic Partnership	9	12%	21	24%
Married	54	69%	48	55%
Divorced	1	1%	1	1%
Not reported	7	9%	8	9%
Provisional Diagnostic Status				
Major depressive disorder	38	49%	40	46%
Bipolar I disorder	3	4%	5	6%
Bipolar II disorder	0	0%	1	1%
Persistent depressive disorder	8	10%	10	11%
Panic disorder	14	18%	7	8%

Agoraphobia	8	10%	12	14%
Social anxiety disorder*	7	9%	18	21%
Obsessive compulsive disorder	15	19%	18	21%
Generalized anxiety disorder	18	23%	23	26%
Posttraumatic stress disorder	9	12%	11	13%
Alcohol use disorder	1	1%	2	2%
Cannabis use disorder	1	1%	1	1%

*p<.050 baseline difference between group; Note: percentages are based on the available data for each variable (e.g., some participants did not provide complete diagnostic data).

Table 2

Comparison of PPC and STAND Interventions

Intervention Feature	**STAND**	**PPC**
Clinicians: training and supervision	Clinical care for severely depressed/suicidal patients was provided by advanced clinical psychology PhD students trained by licensed clinical psychologists via didactics and role plays, with weekly supervision	Care for all patients was provided by psychiatry residents trained by psychiatrists with specialty in reproductive psychiatry via didactics, with weekly supervision/staffing of cases
Coaches: training and supervision	Coaching for digital therapy for moderately depressed patients was provided by bachelors' level certified coaches, and clinical psychology PsyD and PhD students who were trained by licensed clinicians in CBT components of the digital therapy program and strategies for supporting digital therapy; weekly supervision was provided	n/a
Frequency of CAT-MH assessment	Weekly assessments Rationale: Measurement-based care, to inform: adaptation of care between digital therapy with coaching (for moderate symptoms) and clinical care (for severe symptoms or SI risk); shift therapeutic approach within clinical care; alert for SI risk detection and management	Bi-weekly assessments Rationale: Still more frequent than typical community-based care, this allowed for comparison between conditions on repeated measurements of symptom outcomes. Not used for measurement-based care.
Prescribed Number of Sessions	*Digital Therapy with Coaching* First half of study (TWU digital therapy): 3 core + 6 optional digital modules, plus up to 9 coaching sessions. Second half of study (DGC PND digital therapy): 5 core + 5 optional digital modules, plus up to 10 coaching sessions *Clinical Care* Measurement-based model with, number of sessions guided by symptom severity	Intake evaluation and up to 3 visits with supportive therapy and medication management visits. In line with best practice, psychiatrists bridged care until patients established care with outside providers.
Components/Modalities of Treatment	Digital therapy + coaching tier (for moderate depression): digital multi-component CBT adapted for PND	Supportive therapy based on Rogerian principles (e.g., active listening, positive

	population, with coaching support Clinical care tier (for severe depression/active suicidality): individualized, modular, process-based approach to CBT based on functional assessment, with the option for medication management *(using the same medication decision-making as that of PPC).*	regard, other non-specific therapeutic skills). No CBT or other active therapy modalities were used Medication management in line with best practices for PND. Psychiatrist transferred care once stabilized on medication, as soon as possible.
Tier Switching	**If in digital therapy + coaching: two consecutive weeks of severe CAT-MH depression score → move to Tier 3 (clinical care) If in remote monitoring (following completion of acute phase of treatment): CAT-MH depression score that increased ≥30% from score at treatment completion and exceeded mild range → offered care (either digital therapy + coaching or clinical care, depending on score)	N/A
Referrals	N/A	Resources included local therapists, social workers and psychiatrists, community clinics, support groups (online & in person), crisis centers, crisis hotlines, multilingual clinical services, financial assistance resources, parenting resources, & newborn supplies resources

*See Wolitzky-Taylor et al. (2023) and Wolitzky-Taylor et al. (2024) for details

**See supplement for details

***Figure 1**: Consort Diagram*

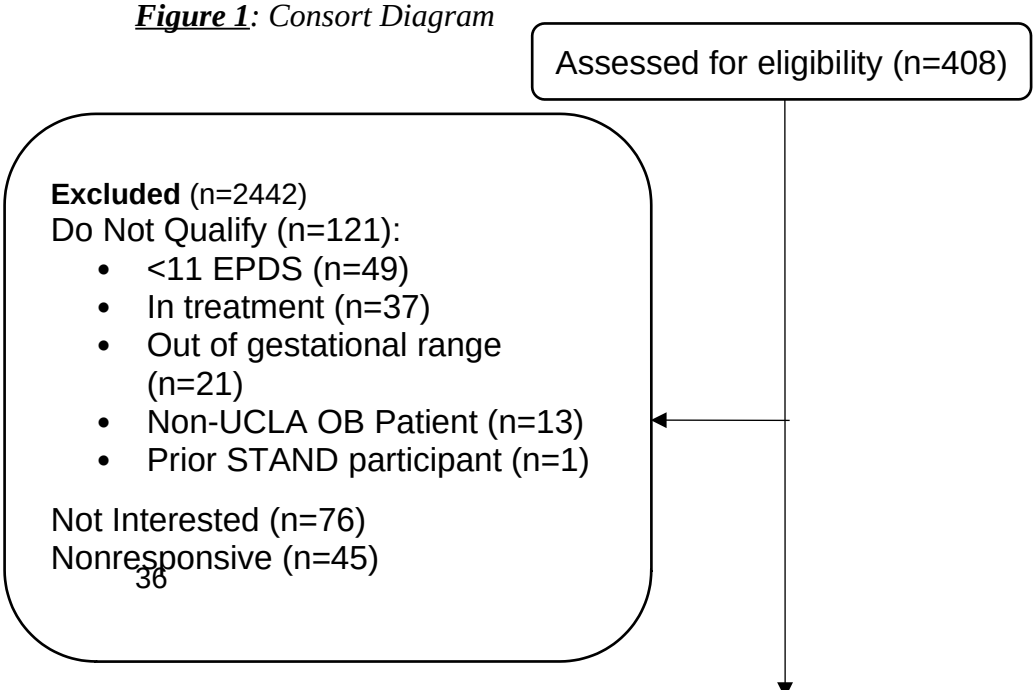

Figure 2. *Changes in CAT-MH Depression (Panel A), EPDS (Panel B), CAT-MH Anxiety (Panel C), and SDS Functional Impairment (Panel D) across Weeks for PPC and STAND*