Evaluating Technology Enabled Services in Perinatal Depression

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PROTOCOL TITLE: Technology-Enabled Services to Support Care Mangers in Obstetrics Clinics to Treat Perinatal Depression

SHORT TITLE: Evaluating Technology Enabled Services in COMPASS

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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	
IND / IDE / HDE #	
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☒ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	85
Funding Source	National Institutes of Health
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☒ Yes ☐ No

OBJECTIVES

The aim of this study is to test a Technology Enabled Service (TES) to support the treatment of depression in the context of a collaborative care service (called COMPASS) in the Northwestern Medical

obstetrics clinics. The TES consists of digital technologies that connect patients to Care Managers remotely, providing tools for monitoring patient symptoms, communication, and delivery of a digital intervention.

We will compare the TES to an eTreatment As Usual (eTAU) consisting of current care plus access to a website [http://compass-care.northwestern.edu/] that will provide content specific to perinatal depression.

We will utilize a randomized clinical trial (RCT) to compare a technology enabled service (TES) intervention to enhanced treatment as usual (eTAU) within antenatal and postpartum women. Randomization will occur at the patient level. It is not feasible to mask participants or providers.

The primary effectiveness outcome is depression severity. Secondary outcomes are anxiety, and satisfaction with care.

Aims
Aim 1: Conduct a pilot Optimization-Effectiveness-Implementation (OEI) hybrid trial of a Technology Enabled Service (TES) for the treatment of depression compared to enhanced treatment as usual (eTAU).

Aim 2: Experimental therapeutics aims. Analyses will explore the mediating effects of the CM dashboard features that support the CM's treatment activities and workflow, including tracking symptom response, managing the stepped care processes, and communicating care plans. We will also explore the moderating effects of race, ethnicity, income, age, anxiety symptom severity, and mobile phone competence on the depression outcome.

BACKGROUND

Note: The "Background" section has been significantly reduced to create a more succinct protocol document. The original grant submission with the full background information is available upon request.

1. Perinatal depression is common and associated with adverse maternal and child outcomes.[1-5]

Glossary of Terms:

a. **Perinatal:** relating to the time, usually a number of weeks, immediately before and after birth.
    a. **Antenatal:** before birth; prenatal.
    b. **Postpartum:** The period just after delivery, as with postpartum depression. Postpartum refers to the mother, and postnatal to the baby.

2. Myriad barriers to effective treatment exist.[6-11]

3. Collaborative Care (CC) represents an innovative health systems approach to depression treatment.[12-20]

4. Perinatal Depression poses unique care challenges.[21-22]

5. Significant gaps exist in Perinatal CC implementation.[23-26]

6. Technology enabled services (TES) may offer a solution for effective Perinatal CC delivery.
TESs can (a) include dashboards/interfaces to automate Care Manager (CM) tasks and streamline CM workflows for population-based case review; (b) connect the CM to both patients and providers, facilitating communication about stepped care among the entire care team; and (c) directly deliver digital treatments to people who are unable to engage in person due to logistical barriers common in the Perinatal period. Smartphones are broadly available among reproductive aged people and are owned by 94% of Americans under age 30 and 89% ages 31-49.[27-29] Several RCTs have shown that digital interventions delivered through smartphones are effective in reducing Postpartum Depression.[30] As such, a TES can integrate a seamless service in which adherence to the core tenets of CC are facilitated by

digital technologies, but this novel application of TES has not been previously studied.

STUDY ENDPOINTS
We will utilize a pragmatic, RCT based on our OEI hybrid trial design.[53-55] A total of 85 people (75 from Northwestern and 10 from Women and Infants Hospital) will be randomized to either TES or enhanced treatment as usual (eTAU). Descriptions of the TES and eTAU interventions appear in the next section labeled "Study Intervention(s)/ Investigational Agent(s)." Depressive symptoms and other outcomes will be measured at baseline and at 6 and 12 weeks. Beyond 12 weeks, participants will be allowed to continue use of the TES app and the eTAU website for the duration of the grant-funded budget period. App and website use will be tracked for the entire study duration.

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S)
Participants will be assigned to receive one of two study interventions: (1) a Technology Enabled Service, or (2) Enhanced Treatment as Usual. The design of the TES and eTAU interventions were determined through the design study (STU# STU00211314) and negotiations with our software development contractor (Adaptive Health).

Technology-Enabled Service (TES)
The TES will be based on Adaptive Health's IntelliCare platform (described below). The TES will permit use of text message communication. Text message content will meet HIPAA standards, and will not contain information that might identify the patient as being in treatment for depression. Text message communication may be used to encourage IntelliCare app use or arrange phone calls to avoid risk of loss of confidentiality.

IntelliCare
The IntelliCare intervention consists of 2 components: (1) a patient-facing app for assessment and self-management of depression, (2) a Care Manager dashboard. A brief description of each component appears below:

1. Patient-facing app: The patient-facing app contains the following tools for the assessment and self-management of depression:
    - Assessment: Within the IntelliCare App, participants will be prompted to complete an assessment of current (within the prior 2 weeks) depressive and anxiety symptoms.
    - Self-management: IntelliCare depression and anxiety self-management modules will be used in the trial. Each module represents a single behavioral strategy (e.g., scheduling positive behaviors, thought restructuring, goal setting), and takes only a few seconds to use. The modules address specific treatment goals, and may include instructional content as well as interactional components (e.g., activity scheduling/monitoring, thought records) that support behavior change. All participants will download the main app onto their own phones and will be encouraged to use the modules as directed by the CM throughout the study period.
2. Care Manager Dashboard: The CM dashboard displays which modules are being used by which patients, supporting efficient triage and clinical decision making. The dashboard also includes mental health assessment scores, a place to document notes about patient interactions, and a text messaging interface.

Enhanced Treatment as Usual (eTAU)
The eTAU will consist of current care plus access to a website (compass-care.northwestern.edu) that will provide content specific to perinatal depression. Patients randomized to eTAU will communicate with their Care Managers using phone or MyChart, which is consistent with standard clinical practice.

PROCEDURES INVOLVED
This is a multi-pronged prospective investigation of a TES to improve collaborative care service delivery to people with perinatal depression. Participants will be enrolled in a pragmatic RCT with outcome assessments at baseline, 6 and 12 weeks.

Data will be gathered from study participants as outlined in the table below. We have described how data collection methods differ by randomization assignment where applicable.

Table 1. Effectiveness Measures

Outcome/Construct	Measure Name	Method	Timing
Depressive and suicidality symptoms	PHQ-9 with BDI	TES: data gathered via IntelliCare and REDCap eTAU: data gathered routinely for COMPASS clinical care CMs or research team will enter these data in the study database.	Continuous
Anxiety symptoms	GAD-7	TES: data gathered via IntelliCare and REDCap eTAU: data gathered routinely for COMPASS clinical care CMs or research team will enter these data in the study database.	Continuous
Suicidal ideation	Columbia Suicide Risk Assessment	Data gathered routinely for COMPASS clinical care by Care Managers or research team and entered in the study database by the CM or research team	As needed
Demographics	Demographics Questionnaire	Participant self-report survey	0w
Health status	SF-36 (3 items)	Participant self-report survey	0w
Other mental health treatment	"Other Mental Health Treatment" Questionnaire*	Participant self-report survey	0w, 6w, 12w
Technology engagement, usability, usefulness, and satisfaction	TWEETS	Participant self-report survey	6w, 12w
Mobile phone competence	Mobile Phone Competence	Participant self-report survey	0w
Bond between patient and CMs	Working Alliance Inventory / Short Revised (WAI-SR); (BOND ONLY)	Participant self-report survey, Care Manager data entry	6w, 12w
Supportiveness of CMs	Supportive Accountability Inventory	Participant self-report survey	6w, 12w
Satisfaction with services	SIMH	Participant self-report survey	6w, 12w
Coaching user feedback	Coaching user feedback survey	TES only: Participant self-report survey	6w
	Coaching user feedback interview	TES only: Optional participant telephone interview	6w
Usability Interview	Usability Interview	TES only: Optional participant telephone interview	2w, 4w, 6w
Alcohol and Substance Use	Substance use information in the EMR	Medical records	Continuous
Comorbidities	Diagnoses from the EMR	Medical records	Continuous
Obstetrics information	Actual delivery date, complications in pregnancy, gestational age at delivery	Medical records	Continuous

Adherence	App/website usage, communication with CM	TES: app usage and text message data gathered by IntelliCare and transferred to the study team eTAU: website usage data gathered via website analytics tools	Continuous
Execution of Stepped Care	Each time the PHQ-9 score is documented, the CM or the research team will indicate whether the stepped care protocol was executed in response to PHQ-9 total score.	Data gathered routinely for COMPASS clinical care. CMs will enter these data in the study database when documenting PHQ-9 scores.	Continuous

Self-report surveys and Care Mzanager data entry forms have been uploaded to the eIRB+ system for review. Please see the data handling section for a description of the procedures that will be used to obtain data from self-report surveys, interviews, CM data entry, medical record data extraction, IntelliCare data, and COMPASS website usage data.

DATA AND SPECIMEN BANKING
Deidentified data will be stored indefinitely for secondary analyses.

STUDY TIMELINES
Enrollment Timeline
Recruitment for the clinical trial will occur outside the context of usual Care Manager (CM) activities and will be managed by the research team with support from the Care Managers (CM). All patients judged as meeting perinatal depression or anxiety criteria by the research team who are at least 18 years of age will be offered participation and will be screened verbally by the research team and/or Care Managers (CM). If participants screen eligible, they will be directed to a digital version of the consent form, as described on Pg. 12. The research team will record the results of all recruitment contacts. We expect to enroll 100 participants through March 2024.

Timeline of Participant Activities
Active participation will last 12 weeks for each study participant. Participants will use the study interventions during the 12-week period and complete assessments according to the schedule laid out in table 2 below:

Table 2. Participant Activities

Method	Week 0	Week 2	Week 4	Week 6 Mid-Treatment	Week 12 End of Treatment
Self-report Survey	x			x	x
Usability Interview (optional)*		x	x	x	
Coaching User Feedback Interview (optional)*				x	
App and Website Usage	Continuous, unobtrusive				
Communication with Care Manager	Continuous, unobtrusive				
Medical Record Data	Continuous, unobtrusive				

* Optional Usability/User-Feedback Interviews (2w, 4w, 6w)
Participants will be informed during the informed consent process that they may be invited to complete optional interviews. All interviews will be conducted by telephone. At the end of week 1, participants will be asked if they would like to provide additional feedback about their experience using the IntelliCare app

and working with the study coach via paid interviews. Participants who express interest in providing feedback will be contacted by study staff to schedule the optional interview session(s). More information about the nature and timing of the optional interviews is provided below.

IntelliCare app usability interviews (2w, 4w, 6w)
As we begin enrolling the clinical trial, we will invite the first participants randomized to the TES condition to provide feedback on the usefulness and usability of the IntelliCare application. These optional interviews will be administered to approximately 10 participants.
The app usability interview guide has been uploaded to the eirb+ portal for review.

Coaching user feedback interviews (6w)
All participants randomized to the TES condition will be invited to share additional user feedback about their experience working with the Care Manager/coach at the week 6 (mid-treatment) timepoint.
The coaching user feedback interview guide has been uploaded to the eirb+ portal for review.

The anticipated completion date for primary analyses is March 31st, 2025.

INCLUSION AND EXCLUSION CRITERIA:
Eligibility will be assessed by the research team and Care Managers (CM) via a verbal screening survey. The screening survey has been uploaded to the eIRB+ system. All patients ages 18 years or older with a smartphone who are referred or eligible to receive COMPASS care management for mental health care while pregnant or within 3 months of delivery will be offered study participation.

Inclusion Criteria: US Citizen/Resident (for payment purposes), English speaking, 18 years or older, referred to COMPASS for mental health care, currently pregnant and currently parenting or within 3 months of delivery, has mild to severe perinatal depression (defined as a PHQ-9 screen $\geq$5) or moderate to severe anxiety (defined as GAD-7 screen $\geq$ 5), owns a smartphone, has used smartphone in last 7 days
Exclusion Criteria: Has experienced a pregnancy loss (miscarriage, termination, or stillbirth of the index pregnancy)*, has severe suicidality (as defined by the presence of a plan and intent to act on that plan), not parenting their child (i.e. adoption, foster care, etc.), anyone not meeting the inclusion criteria described above

*If a participant experiences a pregnancy loss during the trial, they will remain in the COMPASS program but they will be asked to stop using the app.

VULNERABLE POPULATIONS
This research will not impact the course of the pregnancy or health of the fetus. Our interview questions and assessments will not ask about the health or viability of the fetus, nor about decisions the client must make related to the health or viability of the fetus.

RECRUITMENT METHODS
Recruitment for the clinical trial will occur outside the context of usual Care Manager (CM) activities and once a participant is randomized, it will be fit into normal processes of care, to make the results as generalizable as possible. Patients may be identified a) during regular CM visits or b) through rosters pulled using Electronic Medical Records. All patients judged as being either pregnant or within 3 months of delivery who are at least 18 years of age will be given an electronic or verbal description of the study by the Care Manager or research team and screened for eligibility. Some patients may be given a flier/sent an email/sent a MyChart message with more information about the study before initiating the verbal screening procedure. CMs and the research team will record the results of all recruitment contacts.

All recruitment advertising materials have been uploaded to the eIRB+ system for review.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES
We will reimburse all trial participants for completing research assessments.

All subjects can earn up to $100 for completing online study assessments. Reimbursement for each completed assessment is outlined in table 3 below.

Table 3. Compensation for Completion of Online Surveys (All Participants)

Method	Week 0	Week 6	Week 12	Total
Self-report Survey	$20	$30	$50	$100

Week 0 will be paid after randomization and welcome call. Week 6 and week 12 will be paid upon survey completion.

Subjects randomized to the TES arm can earn additional compensation if they are interested in completing the optional user feedback interviews. Compensation for each interview completed is outlined in table 4 below.

Table 4. Compensation for Completion of Optional Interviews (TES Arm Only)

Method	Week 2	Week 4	Week 6	Total
App Usability Interview	$25	$25	$25	$75
Coaching Feedback Interview			$25	$25
Total	$25	$25	$50	$100

Depending on Northwestern University payment guidelines and availability at the time of participation, payments to participants will be issued in one of the following ways:

- Gift card: The following gift card payment methods are available to participants earning no more than $100 per calendar year:
  - Amazon.com gift card: Participants will be sent a code via email that will allow them to redeem an Amazon.com gift card. Gift Cards may only be redeemed toward the purchase of eligible goods and services provided by Amazon.com. Participants must create an account with Amazon to use the card. No fees apply to Amazon Gift Cards and the balance will not expire.
  - PNC Stored Value (Visa) Card: If participants do not have an Amazon account or do not wish to be compensated through Amazon, they may request a Stored Value (Visa) Card instead. The cards may be virtual or physical as per participant preference.
- Check: Participants earning more than $100 per calendar year must be paid by check. Checks require a signed W9 form. The check may be mailed to the participant's address.
- Through Northwestern University (NU) Payroll if the participant is an NU employee

Participants will be informed that it will take approximately 2-4 weeks for payment to be processed.

WITHDRAWAL OF PARTICIPANTS

Patients can discontinue the TES and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

Patient voluntarily withdraws from treatment (follow-up permitted);

Patient withdraws consent (termination of treatment and follow-up);

Patient is unable to comply with protocol requirements; (termination of treatment and follow-up);

Patient demonstrates disease progression (termination of treatment and follow-up);

Note: Care Managers regularly monitor depressive symptoms as part of routine care. They will make a referral for additional mental health treatments as needed. Most patients remain in collaborative care as a means to support and coordinate their ongoing mental health care.

However, if a patient requires psychiatric hospitalization, a partial hospitalization program (PHP), or an intensive outpatient program (IOP), they are taken out of the collaborative care program. Aligning with this standard clinical care, study participation will end if a patient requires hospitalization, PHP, or IOP care. The study team will continue to utilize the data previously collected for analysis purposes.

Patient experiences a pregnancy loss during the trial (follow-up permitted).

RISKS TO PARTICIPANTS

Potential Risks

The proposed study poses minimal risks. All potential risks associated with participation in this study will be disclosed in consent documents. Any potential risks that might exist fall into four categories: (a) risks associated with the intervention; (b) risks associated with research assessments, consisting of questions about depression, anxiety, and personal functioning, and other mental and emotional problems; (c) risks associated with potential loss of confidentiality; and (d) risks of worsening mental or emotional state. We address each in turn below.

Risks of the intervention: TES intervention programs generally have not been shown to cause any harm. The primary risk of the intervention is participants being distracted by their mobile phones while engaged in activities that demand their complete attention. Participants occasionally try to use mobile apps while driving motor vehicles, and therefore will be instructed during the intervention onboarding process to never to use the mobile phone while driving. Participants will be made aware of the physical, financial, and legal risks associated with using the phone while driving. If the research team becomes aware of a participant engaging in this behavior, the PIs will consult to determine the most appropriate way to eliminate this risk.

Risks associated with research assessments: Research assessments include questions about depression and other mental and emotional problems. Participants will give voluntary responses to interview questions; they are told that they can decline to answer any questions that they choose. The instruments and methodologies are well tested and are not known to cause problems or distress on the part of the participants. All research interview based assessments are audio-recorded, for the purpose of review to ensure quality assurance ratings of assessment performance, including ensuring that patients are comfortable with the interview procedures. Audiotapes will be maintained on a secure server with no identifying information in the labels for the duration of the funded study, unless other arrangements are made. On occasion patients may request that audio files be deleted before the end of the study, in which case we will comply.

Risks associated with potential loss of confidentiality. There is a slight risk of loss of confidentiality. While communication occurs within Adaptive Health's secure messaging platform, there is some possibility that others may see the participant's open webpage or smartphone. There is also a small possibility that databases may be hacked, even though they are behind secure firewalls. Measures to protect security in these instances are described below. Confidentiality may be broken by research staff to ensure the patient's safety if there is an imminent threat to self or others. There is also the remote possibility that research records will be subpoenaed by a court of law. All of these potential losses of confidentiality will be disclosed in the consent documents.

Risk of Suicide: The development of suicidal ideation during the study remains the most serious risk. However, this risk is inherent in the population and would occur whether or not participants were enrolled in the study. It is not believed that this risk, or other adverse outcomes are increased as a function of being enrolled in this study.

All potential risks associated with participation in this study will be disclosed in consent documents. All patient participants will continue to receive all care through their obstetric and collaborative care providers within Northwestern Medicine. Thus, the full range of available treatment options are available to participants, including antidepressant medications, psychotherapy, electroconvulsive therapy, or inpatient treatment. The benefits of these alternatives are that they are evidence-based, more intensive and

specialized. This study imposes no restrictions on the participant in terms the use of other treatments. As this is a pragmatic study, all treatments available to the individual in the Northwestern Medicine system will remain available during study participation.

Protection Against Risks

Loss of Confidentiality: No data will be collected until staff has completed human subjects training and IRB approvals have been obtained. Aside from on the written informed consent, names of participants will not appear on any written records, including interview forms, survey forms, and checklists. All research data will be electronically recorded and stored in Research Electronic Data Capture (REDCap) tools hosted at Northwestern University. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Data communication between data entry computers and database servers will be encrypted via a VPN client. Access to the VPN connection will require user authentication via username and password. Firewall software will restrict communication to the database server that is absolutely critical for conducting research. The databases and all data entry procedures will be designed to maintain the confidentiality of patients enrolled into the study. Numbers will be used to identify all written study materials, and no personal identifiers will be on such materials. Hard copy files will be stored in a secure double-locked room accessible only to the study team. Audio and video data will be stored on secure servers and will only be available for coding by study staff. Adaptive Health, the software vendor involved in this project, will follow data security guidelines as specified in the Master Service Agreement between Northwestern University and Adaptive Health.

To reduce the risk of loss of confidentiality through the participant's device, we will instruct patient participants on how to add a PIN to their phone to prevent unwanted access. We will clearly inform the patient participants of the risk of data insecurity.

Additionally, Dr. Miller and all members of the research team have been fully trained in research conduct, including completing the NIH-required Good Clinical Practice Training.

Emotional Discomfort: Participants will be informed that their participation in the study is entirely voluntary and that they may stop at any time without affecting their access to medical care. Participants will be told that they may decline to answer any questions or complete any procedures.

Plans for Ensuring Safety and Suicide Prevention: The development of suicidal ideation during the study remains the most serious risk. Patient safety always takes precedence over study protocol. All suicidality procedures are managed directly by the patient's care management team or through research staff including Joshua Santiago, Nathan Winquist, and Shannon Smith. The CMs are licensed clinical social workers who have completed Mental Health First Aid trainings and have been trained in suicide risk management as part of their regular job duties. CMs are buttressed by the COMPASS psychiatrists, the obstetricians, and the Asher Center (see Letter of Support from Dr. Wisner) who are available for clinical support. Research staff are trained in suicide risk management as part of their regular job duties. Research staff are buttressed by clinical psychologists and are available for clinical support.

There are a number of pathways through which suicidal risk can be detected. During the trial phases, suicidality is detected through automated PHQ-9 self-report assessments, direct communications with the Care Managers via phone or messaging (email, text, etc.), or direct communication with research staff during user feedback interviews. In each of these instances, the goal is to rapidly acquire additional information that can trigger safety procedures if necessary. When suicidality is expressed by the participant directly to the research staff in a usability interview or other direct communication, the research staff follows up to conduct a risk assessment based on the Columbia Suicide Severity Rating Scale and engage the participant in risk management procedures based on their risk status.

All participants in the trial or pre-enrollment receive automated self-report assessments. If a participant rates Question 9 of the Patient Health Questionnaire-9 (i.e., "Over the last 2 weeks, how often have you

been bothered by thoughts that you would be better off dead or of hurting yourself in some way") a 1 or higher, a second suicidality question from the Beck Depression Inventory (BDI) is administered that is more specific in identifying suicide risk. Participants who indicate that they would like to kill themselves, or would kill themselves are considered "at risk." All CMs are notified via an alert in the TES and/or by the research team directly via email within one business day. The first CM to receive the notification will call the patient for a risk assessment based on the Columbia-Suicide Severity Rating Scale by phone within one business day. If an acknowledgement is not made by a CM, a member from the research team or clinical supervisor will follow up with the CM. Once acknowledgement is made by the CM, the Columbia-Suicide Severity Rating Scale is conducted as a routine part of clinical care. For patients who are at greater than low risk, the CM takes all necessary actions to ensure the safety of the patient, including considering the use of psychiatric hospitalization. If the patient does not respond to contact attempts from the CM, the patient's medical emergency contact, on file for all COMPASS patients, is called to assist in contacting the patient. In the rare event that contact cannot be made, CM's may contact emergency services for a wellness check in accordance with COMPASS procedures. When suicidality is expressed by the patient directly to the CM, the CM similarly follows up to conduct an evaluation and perform safety procedures. Perinatal psychiatrists are available for consultation with CMs and for follow-up consultation with any patient perceived to be at risk. For patients who are not at immediate risk and who do not require hospitalization, an outpatient psychiatric evaluation may be coordinated by the CM. A member from the research team or the clinical supervisor will follow up if the CM does not within two business days.

We note that these are risks inherent in the population and would occur whether or not they were enrolled in the study. We do not believe that the risk of these depressive, suicidal, or other adverse outcomes are increased as a function of being enrolled in this study or receiving TES during the trial phases. All potential risks associated with participation in this study are disclosed in consent documents.

Limits on Confidentiality of Clinical Information: In accordance with standard of care practices in mental health, confidentiality is limited in cases when the participant presents as a danger to themselves or to others (e.g., situations of physical abuse, neglect, suicidality). If the participant reports imminent suicidality or homicidally during any portion of the trial, they will be hospitalized in the appropriate mental health facility with input from the perinatal collaborative care team (either voluntarily or involuntarily).

POTENTIAL BENEFITS TO PARTICIPANTS

There is no direct or immediate benefit to participants from whom data will be collected, although we anticipate some participants may receive perinatal depression support through the TES. The participants enrolled will receive a modest recognition of their time in accordance with their phase of participation. The risks to subjects are minimal in this observational study.

DATA MANAGEMENT AND CONFIDENTIALITY

Below, we describe the data management strategy for the range of data collection methods involved in this project.

Self-Report Surveys (REDCap)

All participant self-report survey data will be electronically recorded and stored in Research Electronic Data Capture (REDCap) tools hosted at Northwestern University. REDCap is a secure, Web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Data communication between data entry computers and database servers will be encrypted via a VPN client. Access to the VPN connection will require user authentication via username and password. Firewall software will restrict communication to the database server that is absolutely critical for conducting research. The databases and all data entry procedures will be designed to maintain the confidentiality of patients enrolled into the study.

Care Manager and Research Team Data Entry

Care managers and the research team will be trained to routinely enter data from anxiety, depression, and suicidality assessments in the REDCap study database. Care managers will only have access to

certain data entry forms in the database, and will not be able to access data from participant self-report surveys or interviews.

Interview Data
Audio recordings of interviews will be stored on the secure FSM ResFiles server. Interview audio files may be transcribed by the following NU transcription vendor: GMR Transcription, https://www.gmrtranscription.com/
Audio files will be shared with GMR Transcription through the vendor's proprietary web-based application for secure file management. The resulting transcripts will be stored on the secure FSM ResFiles server and accessed by study team members for coding purposes.
Numbers will be used to identify any written study materials, such as interview notes, and no personal identifiers will be on such materials.

TES Intervention Data Gathered by Adaptive Health
All IntelliCare intervention data will be gathered and securely managed by Adaptive Health during the trial. Per the terms of the Master Service Agreement that is in place between NU and Adaptive Health, at the end of the trial, Adaptive Health will transfer study data to the NU team and delete all identifying information. Table 5 below includes a description of the data elements that will be handled by Adaptive Health.

Table 5. Data Elements Handled by Adaptive Health

IntelliCare System Component	Data Elements Handled by Vendor
IntelliCare App	Identifiers (e.g. email address) to generate user login and create a unique ID that will then follow each user, app use event data (e.g., number of logins, time spent reviewing written information in the app), survey responses (PHQ-9, GAD-7, and suicidality assessment questions), and patient-entered information (e.g. journal entries).
IntelliCare Care Manager Dashboard	Dashboard usage use event data (e.g., number of CM logins, time spent reviewing records in the dashboard), CM notes about study participants (including a field to document participant names for accurate identification of patients in the dashboard).
Text Message Communication	Phone number used to facilitate sending/receiving text messages between study coach and participant, log of messages exchanged between study coach and participant

Links to Adaptive Health's privacy policy and terms and conditions are provided below:
https://www.adaptive-health.com/privacy
https://www.adaptive-health.com/terms

The NU research team will receive routine data exports from Adaptive Health as part of our data quality assurance strategy; exports will be received using secure data transfer methods and data from the exports may be stored on FSM servers and in NU's instance of REDCap.

eTAU Website Use Data
The study team will use google analytics or a WordPress plugin to track website usage amongst participants assigned to the eTAU arm. We may store email addresses in order to establish user accounts that would enable tracking of more granular website usage data (e.g. exactly which pages were visited and how long participants spent reviewing each page). The website is hosted on the NU domain, and any plugins used to track usage would be enabled using NU's instance of WordPress. Only study team members who are granted access to the WordPress site or Google Analytics site will be able to access usage data.

Medical Record Data
The study team will work with an EDW analyst to generate reports containing the following data elements:

- Clinical Data
  - Medical history (including obstetric information)
  - Problem list (which may include things like HIV testing results, substance abuse information, and mental health information)
  - Records about medication or drugs
  - Mental Health information: mental health diagnoses and assessment information, and information about encounters with mental health providers.
- Billing Data
  - Number of minutes billed for care management services during study period

If we are not able to obtain this information via the EDW, a member of the study team with front end NMHC Epic access or backend Epic power user access may extract this information from participants' medical records.

Deidentified information will be transferred into a study database. This de-identified information will be stored separately from any identifying information.

Data Analysis Plan

Effectiveness analyses will use intention to treat methods. To compare overall effectiveness, generalized linear mixed models (GLMM) will be used to determine if there are differences in effectiveness between individuals receiving TES and eTAU over time. Missing data will be examined for potential non-ignorable mechanisms, and will be managed through multiple imputation. Additional covariates will also be included to identify any substantive changes in the service, technologies, and/or implementation plan as a result of optimization. We will examine moderation of treatment arm by strata (postpartum or antenatal), and present results within each strata.

Moderation of TES on effectiveness. We will examine any moderation of the effect of treatment arm on depressive symptoms by race, ethnicity, age, health status, substance/alcohol use, mobile phone competence, or other mental health treatments, in individual GLM models, by estimating a treatment by moderator interaction in predicting end of treatment depression scores adjusting for baseline levels of depression.

Power. Although a pilot study, we provide an estimate of effect that we can detect with 100 randomized participants, as well as within strata of 80 and 20. As power calculations for repeated measures involve correlations over time which are speculative at this point, we provide effect size estimates for 12 month PHQ-9 scores based on an independent t-test. We have 80% power to detect an effect size of 0.58 for the entire cohort – a difference in PHQ-9 scores between eTAU and TES of 2.9 assuming a SD of 5; and effect sizes of 1.41 and 0.65 in antenatal and postpartum populations, which correspond to differences of 7.03 and 3.26 on the PHQ-9).

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

Data and safety monitoring of participants will be monitored by the Principal Investigator, Dr. Miller, who have primary responsibility for monitoring and will do so on a weekly basis during their planned meetings. Dr. Miller will regularly review all data and adverse events and will report all serious adverse events to the Northwestern University Institutional Review Board Requirements. Second, any reporting of significant mental or physical health-related symptoms by the participant to the study team will result in appropriate referrals to the participant's clinician or other appropriate facilities.

The PIs, with the support of the entire research team, will follow procedures outlined under the "Protection of Human Subjects" document that will serve as part of the quality control process for data confidentiality. The PIs will engage with the study team and case managers on a regular basis to ensure data accuracy and protocol adherence.

To ensure the validity and integrity of study data, the PIs, assisted by the Center statistical team, will oversee data management and data checking. Study data are accessible at all times for the PIs, the biostatistician, and all relevant Co-Is to review. The biostatistical team and study manager will conduct

analyses of accrual, drop-outs, protocol deviations on a monthly basis initially, which may drop to quarterly once we are confident that procedures are functioning adequately.

Dr. Miller will review adverse events (AEs) and serious adverse events (SAEs) individually in real-time and in aggregate at each DSMB meeting (not less the annually). They will review the information and make judgments on whether the events were study-related and the severity of the adverse event. These events will be recorded on an Adverse Event Form. Depending on the consensus of the review, further action will be taken to revise the intervention to avoid future events or the study will be stopped if significant harm is anticipated. The PIs ensure all protocol deviations, AEs, and SAEs are reported to the IRB and the NIMH program officer according to the applicable regulatory requirements.
For this study, the following standard AE definitions are used:
Adverse event: Any unfavorable and unintended sign or symptom temporally associated with the use of digital mental health interventions, regardless of whether it is considered related to intervention.
Serious Adverse Event: Any AE that results in any of the following outcomes:

- Death
- Life-threatening situation
- Event requiring inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

AEs are graded according to the following scale:

- Mild: An experience that is transient, and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities.
- Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities.
- Severe: An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study uses the following AE attribution scale:

- Not related: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).
- Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.
- Related: The AE is clearly related to the study procedures.

SAEs and specific treatment-associated AEs are reported to the IRB and NIMH program officer within 24 hours.

Data Safety Monitoring Board (DSMB)
The DSMB will be chaired by Greg Simon, MD, from Kaiser Permanente, Seattle. Dr. Simon is a well-respected mental health researcher. As chair of the DSMB, Dr. Simon will appoint additional board members as needed and will determine the meeting schedule. That said, we expect that the DSMB will meet twice in the first year of the trial and once in the final year. The PIs, Ms. Kaiser, and Dr. Kwasny (biostatistician) will be present to facilitate the flow of information, however they will not be voting members.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS
Potential participants will be identified by the CM. Prior to being consented, candidates will receive information about the study. Candidates who decline the consent procedure or who are screened out will have any identifying information removed from study records. Consent for the study will then be managed by research study personnel, rather than the CM. The study team will not release the identity of any participant to any non-authorized individual, except as is necessary for participant safety or regulatory review.

ECONOMIC BURDEN TO PARTICIPANTS
There will be no cost to participants to receive the TES. It is possible that some participants might have very limited data plans, and the use of IntelliCare apps will cause them to exceed their data limit resulting in fees. IntelliCare apps do not use unusually large amounts of data, so this is an unlikely occurrence, and the study team asks about participant data plans and will inform participants of the expected data usage prior to downloading the apps. There are no procedures that will be billed to insurance.

CONSENT PROCESS
Participants who are referred to the trial by their Care Manager will be verbally screened for eligibility. If participants screen eligible, they will be directed to a digital version of the consent form. The consent form will be administered via Northwestern University's instance of REDCap. Subjects will read through the consent form, answer a series of questions to assess comprehension, and agree to participate by checking a box, typing in their name, and signing electronically. Once the consent is submitted, study staff will review the participant's digital file to ensure that the consent form was signed and the comprehension questions were answered correctly. If a participant answers any of the consent comprehension questions incorrectly, a research assistant will follow up to review that section of the consent form and explain the correct answer. After the consent process is finalized, the participant will be able to access a link to complete the baseline self-report measures along with Instructions for downloading the IntelliCare applications.

NON-ENGLISH SPEAKING PARTICIPANTS
Non-English speaking participants will not be enrolled.

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)
HIPAA authorization language has been included in the study consent form.

The following PHI may be gathered from the patient's medical record:

- Medical history
- Problem list (which may include things like HIV testing results, substance abuse information, and mental health information).
- Records about medication or drugs
- Mental Health information: mental health diagnoses and assessment information, and information about encounters with mental health providers.
- Obstetrics info

Any data that is gathered through the patient's electronic medical records (EMR) will be deidentified. We will store the EMR data separate from the self-report data with identifiers.

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE
The research staff at CBITs have extensive experience conducting remote-delivered mental health interventions. Dr. Miller has experience with successful recruiting and retaining perinatal individuals in longitudinal research studies. With 90 perinatal individuals with PPD currently engaged in COMPASS care along with 30-50 patients referred to COMPASS monthly (conservatively 30% of whom have a primary diagnosis of PPD), successful recruitment into the pilot randomized trial is highly feasible. The COMPASS and CBITs staff have been working closely on the development of this project for several months, and are working to put the resources in place to conduct this study. The services being provided in this study are a supplement to standard care, and the CM will continue to provide all standard care services to patients who enroll in this study.

MULTI-SITE RESEARCH
Table 6. Research Sites and Vendors

Site	Role	Approvals

Northwestern University (NU)	NU will serve as the lead site for this study. Study team members will be responsible for maintaining current versions of the protocol, consent documents, and other IRB materials. NU study team members will be responsible for screening and consenting study participants, collecting outcome data, delivering and supervising the TES, disbursing subject payments, managing suicidality assessments, and analyzing study data. NU staff will facilitate regular project meetings with participating sites and will be responsible for communicating procedural changes, emergent issues, interim results, and study status updates. NU will be responsible for ensuring that all sites involved in data handling have executed the appropriate agreements.	IRB protocol number STU00211815
Adaptive Health	Software Development/Maintenance: Adaptive Health established a Master Service Agreement with Northwestern University to make their IntelliCare platform available for use in delivery of the TES. Data Storage/Retention: Adaptive will store data on their secure servers during the trial and transfer it to NU at the end of the trial. Upon termination of the study, Adaptive Health will erase participant identifiers and retain only de-identified data which will be used to improve the IntelliCare product (per section 19 of the Master Service Agreement).	The following executed agreement between NU and Adaptive Health has been uploaded to the eirb+ portal: Northwestern University and Adaptive Health Master Services Agreement_Fully_Executed.pdf
Women and Infants Hospital (WIH)	Dr. Emily Miller is moving from Northwestern University to Women and Infants Hospital (WIH) on 6/8/22. Dr. Miller will retain her role as primary investigator at Women and Infants Hospital. Dr. Emily Miller has a faculty appointment at Brown University. However, her research is happening at WIH, thus this protocol reflects work that is being done at WIH. One institution will act as external collaborating site: Women and Infants Hospital. Northwestern University will serve as the IRB of Record for each relying site. Site: Women and Infants Hospital Site PI: Emily Miller, MD, MPH Address: Women and Infants Hospital -- Care New England 111 Brewster Street, Building B Pawtucket, RI 02861 Activities to be performing: full research protocol as listed in this protocol. Of note: No activities will occur at an external site until they obtain approval from their local IRB, or the NU IRB and external sites fully execute (complete and sign) a reliance agreement. External study	12/19/2022: The study team received consultation from the IRB. The single IRB letter of support states Brown University, but it was clarified during the consultation that all research activities would take place at Women and Infants Hospital. The IRB has noted this in their files.

	teams will obtain sign-offs or permissions per their local policies. We will provide IRB approval letters from external sites, documentation that IRB review at external sites is unnecessary, or fully executed reliance agreements when available with accompanying protocol updates via modification requests in eIRB+. We will report non-compliance with the study protocol or applicable requirements per local policy.
	
	• Is reliance mandated per federal guidelines or sponsor requirements?
	  o Federal guidelines.
	• If this research is federally funded, who is the prime awardee?
	  o Women's and Infant Health is the prime awardee.
	• Who is the proposed IRB of Record for all participating sites?
	  o Northwestern University.
	• What type of reliance agreement will be used?
	  o IRB Authorization Agreement (IAA)
	• When will institutions or individuals be onboarded? When NU is the proposed IRB of Record, we prefer to review the NU site and overall study scope first, and onboard institutions or individuals in subsequent modifications via fully executed reliance agreements. Onboarding during the initial review process may delay initial approval.
	  o Institutions will be onboarded after this modification is approved. This IRB was initially an approved single-site trial; then, a PI left to another institution (WIH) which is why this is now a multisite study.
	• How will you communicate IRB approval of modifications to study procedures to relying institutions or individuals, and ensure approval before implementation?
	  o Joshua Santiago, Project Manager, will be updating relying sites directly. He has direct access to each relying site IRB system.
	• How will you keep participating institutions or individuals abreast of any problems, interim results, or the eventual closure of the study?
	  o Joshua Santiago, Project Manager, will be the project manager for the relying site and will oversee all research activities; thus, he will be the one providing updates as needed.
	• How will you manage information to protect	

	participants? All institutions and individuals must safeguard data, including the secure transmission of data, as required by applicable local information security policies, state laws, and federal regulations. ○ All participant data will be stored in Northwestern University REDCap and research systems.	

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