Cover Page:

ClinicalTrials.gov#: NCT04566861

Study Protocol and Statistical Analysis Plan: IRB Approved Document

Title: Happy Mother-Healthy Baby: An Anxiety-focused Early Prenatal Intervention **Document Date:** April 1, 2022

JHSPH IRB Research Plan for New Data Collection

Use this template for new data collection and if you also will analyze secondary data. Answer the questions below and for numbered sections that do not pertain to your study, retain the section numbers and bolded questions, and write "N/A". Please start typing in the gray boxes provided.

PI Name: **Pamela Surkan**
Study Title: **Happy Mother, Healthy Baby (HMHB) – Anxiety-focused early prenatal intervention for prevention of common mental disorders in Pakistan: An individual randomized clinical trial**
IRB No.: **9177**
PI Version No. / Date: **April 1, 2022**

I. Aims of the Study: Describe the aims/objectives of the research and/or the project's research questions or hypotheses.

This IRB application focuses on the randomized clinical trial that will be conducted after the formative phase of our research (formative work approved, IRB#7678).

In the primary study, we will evaluate the effectiveness of an evidence-informed, anxiety-focused early prenatal prevention intervention on prevalence of Common Mental Disorders (CMDs) in pregnant women at six weeks' postpartum. We hypothesize that randomization of women with subclinical to clinical levels of prenatal anxiety to the intervention arm will result in fewer cases of CMDs (both Generalized Anxiety Disorder (GAD) and Major Depressive Episode (MDE)) at six weeks' postpartum relative to the routine care arm of mothers with similar levels of baseline anxiety who are not receiving the intervention.

Primary: The primary objective of the trial is to evaluate the effect of an evidence-informed, anxiety- focused early prenatal prevention intervention in pregnant women, compared with usual care alone, on prevalence of Common Mental Disorders (CMDs) at six weeks' postpartum.

Secondary: Secondary objectives include evaluating the impact of the intervention on prevalence of small-for-gestational age (SGA) at birth, preterm birth (PTB) and low birthweight (LBW) as well as the cost-effectiveness of the intervention. We will examine potential mediators of CMDs and whether the effect of the intervention on CMDs and birth outcomes varies by self-reported perceived stress, quality of marital relationship, empowerment, social support, or history of intimate partner violence.

This IRB application also covers a secondary study, to additionally study biological correlates of antenatal anxiety (i.e., immune and endocrine functioning) in a subset of women from the main trial: 200 drawn from our randomized trial (100 intervention, 100 usual care), as well as 100 healthy women without anxiety or depression. The aims of the secondary study are as follows:

Aim 1: To characterize the "immune phenotype" of anxious women across the peripartum, specifically by measuring the relation among anxiety symptoms and peripheral markers of inflammation (IL-6, CCL3, CXCL8, Eotaxin, VEGF, and GM-CSF, as supported by our preliminary data) within and across women (both anxious and healthy) and between those receiving the intervention and control.
Aim 2: To determine the relation between levels of allopregnanolone (ALLO) in pregnancy and 1) concurrent anxiety symptoms and 2) future symptoms of postpartum depression (PPD).
Aim 3: To examine the relation between changes in immune functioning (Aim 1) and ALLO levels (Aim 2) in anxious pregnancy across time.

Aim 4: To examine whether immune function and/or ALLO are mediators or moderators of the association between antenatal anxiety and poor birth outcomes (specifically, preterm birth and small-for-gestational age).

To supplement our study, we will collect qualitative data as part of a process evaluation to better understand women's experiences with the intervention (e.g. how it can be improved). Given the recent effects of COVID-19 on our participants and our study, we will also inquire about how the telephone format of our intervention is being received by our participants, as well as try to learn about the impact of social-distancing and other aspects of the COVID-19 situation on pregnant women generally.

Given the downward trend in the spread of the novel coronavirus in Pakistan, this study will resume with COVID-19 precautions to permit in-person study activities. This includes restricting research team members with COVID-19 symptoms or recent unprotected exposure to COVID-19 persons from working, relocation of most study activities to be conducted outdoors (such as in hospital courtyards), use of disinfectants on all work stations and equipment between study participants, use of face masks and 6 feet of physical distancing, and in cases when being outdoors and/or maintaining physical distancing is not possible, having staff wear appropriate PPE (i.e., face mask and/or shield) and keeping in-person interactions brief and one-to-one when possible. These precautions will apply to recruitment, intervention delivery, and data collection, and when appropriate some study activities (such as more lengthy interviews) will continue to be conducted by phone to help minimize any risks to staff and participants. Additional measures being taken in accordance with guidelines by the WHO and local authorities include encouraging frequent use of hand sanitizer and/or handwashing for twenty seconds, avoiding any unnecessary physical contact such as handshaking, and avoiding congregations of multiple people, especially in contained areas. COVID testing is also available for staff or participants with symptoms or suspected exposure to COVID-19 positive persons.

II. **Background and Rationale:** Explain why this study is being done. Summarize briefly what is already known about the issue and reference previously published research, if relevant.

Common mental disorders (CMDs), referring to depression and anxiety, occur frequently in the perinatal period, often remain untreated, and constitute significant global health issues.(1) The high prevalence of symptoms of prenatal anxiety and depression present challenges for families and pregnancies, especially in resource-limited settings where mental health services are scarce.(2) Negative consequences of CMDs in pregnancy and the postpartum are evident,(3-11) and it is well documented that maternal-child interactions in the postpartum period are critical for optimal child growth and development.(12, 13) While the effects of postpartum CMDs are serious, prenatal anxiety is one of the strongest predictors of postpartum CMDs,(14, 15) is highly prevalent (e.g., affecting between one-third and one-half of women in Pakistan),(16, 17) and is a little studied condition, with the preponderance of epidemiological and intervention studies focused on depression.

The adverse consequences of prenatal anxiety are substantial in their own right; in addition to predicting later anxiety and depression and risk of suicide,(14, 15, 18, 19) prenatal anxiety is related to poor maternal-fetal quality of attachment and negative attitudes towards motherhood,(20) as well as poor infant birth outcomes,(21) child ill health,(22) and developmental problems.(23-27) Research further suggests that adverse effects of anxiety on child emotional development remain, even after taking depression into account.(26) Furthermore, recent studies and reviews report that prenatal anxiety is associated with a range of poor birth outcomes.(21, 28, 29)

Plausible biological mechanisms underlie the effects of prenatal psychosocial stress, related to anxiety, on the fetus. A main proposed mechanism is through increased activation of the hypothalamic-pituitary-adrenal axis.(30) Adverse fetal programming resulting from maternal psychosocial stress occurs very early in pregnancy before fetal brain or nervous system has developed,(31, 32) possibly through placental functioning.(33) The sympatho-adrenomedullary system may also be involved, affecting catecholamine concentrations.(30, 34) Finally, prenatal stress can affect maternal immune status,(35) leading to infections and complications such as intrauterine inflammation, a common cause of preterm birth.

Passive immunity or immune alterations can be transferred to offspring.(36) Prenatal stress may also affect child microbiota, health behaviors in pregnancy (e.g., unhealthy eating, sleep, and physical activity), and epigenetics.(30)

Effective treatments exist, but we lack preventive approaches that could reduce the prevalence of highly damaging CMDs, leading to benefits for the mother and child. Cognitive Behavior Therapy (CBT) is an effective treatment for both anxiety and depression,(37, 38) and combined with strategies to address social stressors, CBT has been used effectively for depression in the later prenatal and postnatal period in low-resource settings.(39) However, it has rarely been used as a preventive intervention, an approach that is vital in low- and middle-income countries (LMICs) where an enormous treatment gap exists in which the most socioeconomically needy populations have the least access to mental health care.(40, 41) As social stressors such as intimate partner violence, lack of social support, and gender imbalance also contribute to anxiety and the high prevalence of CMDs, interventions addressing these issues in early pregnancy are urgently needed, prompting calls for the development of preventive initiatives in limited-resource settings.(42)

Current interventions may start too late in pregnancy to avert poor growth in utero and in the postpartum period. Our prior maternal depression intervention in Pakistan, the Thinking Healthy Program (THP), which started in the third trimester, was likely initiated too late to be able to influence child birth outcomes such as intrauterine growth restriction (IUGR). The effect of prenatal stressors on IUGR are likely trimester dependent; specifically, anxiety or stress in the second trimester of pregnancy appears to increase the risk of small-for-gestational age (SGA) at birth.(43, 44) Furthermore, our third trimester THP intervention did not improve child growth in the first year of life,(39) a finding possibly attributable to the late initiation of the intervention.

Prenatal anxiety is a risk factor for poor fetal growth and preterm birth, common in LMICs like Pakistan. Approximately one-third of infants in LMICs are born SGA,(45) and Asia has the highest global prevalence of SGA and PTB.(46) A recent study reported that newborns of mothers with prenatal anxiety had a three-fold higher odds of poor fetal growth, defined as SGA, IUGR, or both.(29) Two meta-analytic reviews have reported evidence for a relation between prenatal anxiety and LBW and PTB.(21, 28) These important outcomes, reflecting poor fetal growth or shortened gestation, are in turn risk factors for neonatal and post-neonatal morbidity and mortality,(47-50) poor cognitive functioning,(48, 51) and chronic health and social disabilities.(52-55)

Economic analyses in the context of perinatal mental health interventions are valuable but scarce. There is a dearth of economic evaluations for mental health interventions in LMICs, and the few conducted often are of poor quality.(56-58) A 2013 meta-analytic review of 38 studies on use of non-specialist providers for mental health interventions in LMICs reported only three performing any cost-analysis, none of which focused on maternal mental health.(59) Nonetheless, for policy makers, cost estimates for health interventions are urgently needed to ensure budgeting is most effective,(60) especially where mental health service budgets are low.

In LMICs, a striking gap exists between mental health needs and access to care.(40, 41) At the same time, no current prevention interventions address prenatal anxiety in these settings. Its high prevalence, coupled with limited resources for treatment, results in an urgent need to expand the evidence base for preventive strategies.

In Pakistan, 35%(17) to 49%(16) of pregnant women suffer from anxiety. These symptoms tend to persist and strongly predict maternal depression and anxiety disorders postpartum,(14, 15, 61-63) adversely affecting caregiving.(64-68) Along with significant human and economic costs to mothers,(69) prenatal CMDs are associated with poor pregnancy outcomes(70-73) and long-term cognitive and developmental problems in offspring.(23-27, 69, 73) Thus, prevention efforts targeting CMDs early in the prenatal period have enormous potential for reducing the negative effects of postnatal mental disorders on mothers and improving child outcomes.

Our main innovation is a focus on reducing anxiety; while anxiety and depression often co-occur,(74) prenatal anxiety, especially early in pregnancy, has been neglected. Exposure to anxiety, even as early as during the second trimester of pregnancy, is important to intrauterine fetal growth.(43, 44) Given the high prevalence of adverse birth outcomes in

Pakistan,(e.g., 47% of newborns in Pakistan are SGA),(46) this setting provides a unique research opportunity. Contrasting with current initiatives (that do not address anxiety), our proposed intervention specifically targets symptoms of anxiety, using strategies based on CBT. This approach is known to effectively treat CMDs,(37, 38, 75) but it has been underused for prevention in both high- and low-income countries despite evidence-based recommendations.(76) As both clinical and subthreshold prenatal anxiety strongly predicts depression,(15) we expect our anxiety-focused intervention to have carry-over benefits on depression as well as anxiety. By creating and testing an intervention in the early- to mid- pregnancy, we will provide critically needed evidence of the effectiveness of these approaches in reducing prevalence of both of these damaging maternal conditions and their collateral effects on newborns. By targeting pregnant women with subthreshold anxiety while simultaneously including women with high anxiety levels, we aim to both prevent and treat GAD and prevent CMDs (i.e., postpartum GAD and MDE). We will do this using non-specialist providers and integrating the program into tertiary care.

Our secondary study adds biological aims to the main trial described above. Understanding biological mechanisms of perinatal anxiety will advance science and ultimately inform treatment strategies, and can identify targets for intervention: Our study has the potential to suggest malleable biological targets for novel intervention strategies, which could lead ultimately to the refining of therapies. In LMICs, the existing pharmacological strategies for anxiety (anti-depressant medications) are often unavailable, unaffordable, or unacceptable to pregnant women. Psychosocial interventions such as ***HMHB*** may prove to be a more feasible and acceptable treatment approach in LMICs. Studying how one such intervention may be linked to biological effects will give us information about biological mechanisms that can be used in the development of other interventions, either psychosocial or biological (for example, anti-inflammatory nutritional approaches or exercise interventions). This therapeutic approach to psychosocial interventions has been advocated by the NIMH.(1, 2) Thus, even if our intervention were unsuccessful, we may learn about the biological mechanisms of antenatal anxiety, which could inform the design future interventions. Likewise, if the intervention is effective in subgroups (those with low vs, high anxiety, for example; those with higher psychosocial stress; those with additional medical complications), we may be able to understand the presumed mechanisms (and again design future interventions) that may be more appropriately targeted to particular subgroups.

This study will focus on alterations in immune and endocrine functioning as one plausible biological mechanism. While research in pregnancy is sparse, some research has identified heightened anxiety symptoms in those with inflammatory diseases outside of pregnancy, such as colorectal cancer and irritable bowel syndrome.(3-5) There are several mechanisms by which increased inflammation could be related to fear and anxiety. Exposure to stressful stimuli has been shown to activate immune cells to release cytokines and other peripheral inflammatory markers.(6-9) This increased inflammation can be related to HPA axis dysregulation in either direction (up or down), depending on the timing of the stressful stimuli (6-12) – and this dysregulation in turn can be linked to behavioral manifestations and clinical symptoms of anxiety. That this relationship is complicated and bidirectional is evidenced by the fact that glucocorticoids released during HPA axis activation can feed back to attenuate the immune response, and by the fact that behavioral symptoms common in anxious individuals (such as sleep dysregulation, smoking, obesity, and poor nutrition) may also be related to inflammation.(13-18) These likely interactions make the immune system and anxiety key areas of neurobiological research– yet application to the perinatal period is lacking. Those studies that have explored immune functioning and perinatal anxiety in a clinical population have focused on cross-sectional views of individual peripheral immune markers, such as cytokines or antibodies,[19-21] or on the effect of maternal anxiety on child immunity.[22,(22, 23)] It is therefore a central goal of this study to measure levels of pro-inflammatory peripheral serum markers across four time points in pregnancy and postpartum to identify the unique "immune fingerprint" of perinatal anxiety and to consider its relationship to other biological systems. One system that is centrally related to the immune response in pregnancy is the neuroendocrine system. Progesterone (P4) and its metabolites, including allopregnanolone (ALLO), rise dramatically in normal pregnancy.(24) Recent evidence indicates that the increase in ALLO during pregnancy[25-27] is related to immune functioning,[28] and that there is bidirectional feedback between progesterone metabolites and the immune system.[28, 29] Higher levels of ALLO have been linked to decreased production of inflammatory mediators by microglia, decreased production of cytokines by macrophages, and possibly to diminished lymphocyte proliferation.(30) Low levels of ALLO have also been linked to anxiety outside of pregnancy.(31) There is

limited evidence of a relationship between ALLO and psychiatric symptoms in the perinatal period, with Hellgren et al. (2014) [32] finding a correlation between low ALLO and concurrent low mood and our own work finding that pregnancy ALLO predicts the development of postpartum depression.[33]

III. Study Design:

A. Provide an overview of your study design and methods. The study design must relate to your stated aims/objectives. Details will be requested later. If your study also involves analysis of existing data, please complete Section XI, "Secondary Data Analysis of Existing Data" in the last part of this research plan. If your study ONLY involves analysis of existing data, please use the research plan template for secondary data analysis (JHSPH IRB Research Plan for Secondary Data Analysis of Existing Data/Specimens).

A phase 3, two-arm, single-blind, individual randomized clinical trial will be conducted in the outpatient department of Holy Family Hospital (HFH) in Rawalpindi, Pakistan, to evaluate the impact of the HMHB intervention on the prevalence of CMDs at six weeks postpartum. We will enroll 1200 eligible women, individually randomizing them to either the intervention (i.e., HMHB) or control (i.e., routine care with similar frequency/timing of visits). Each woman randomized into the HMHB intervention arm will be assigned to a HMHB non-specialist provider who will deliver six individual and between two and six booster sessions of the HMHB intervention program. Women allocated to the control condition will receive routine care, but with increased contact so that frequency of contact will match between the study arms. The primary endpoint is the combined prevalence of GAD and MDE at six weeks postpartum. Data on outcome measures will be collected at birth, and at six weeks postpartum by a trained assessment team masked to the allocation status of the study participant (single-blind). All analyses will use an intent-to-treat (ITT) approach, using all subjects randomly assigned to intervention or control groups. We will also evaluate mediators and moderators of the intervention as well as the cost-effectiveness of the HMHB intervention compared with control arm.

Our two-arm parallel design is justified given the critical need to develop and rigorously evaluate evidence-informed approaches that may prevent these outcomes. Our choice of comparison group (i.e., women receiving slightly enhanced care above the current standard for antenatal care with regard to number visits, training of medical staff, transportation assistance, and payment for ultrasounds needed in pregnancy) and mode of delivering the intervention (i.e., through non-specialist providers) similarly increase the likelihood that findings from our study will be immediately relevant for policy makers. Our trial has the potential to inform the standard of care in Pakistan and other health systems with similar disease burden and system-level constraints to provision of mental health services.

For the qualitative process evaluation of the main trial, in-depth interviews will be used to explore intervention recipients' experiences of the format and content of the HMHB core and booster sessions. We hope to gain an in-depth understanding of women's experiences with the program (including opportunity/emotional costs of participation) in both the intervention and EUC group. We will also sample women who dropped out to understand their reasons for stopping participation. We will hold focus group discussions with the HMHB therapists who have been delivering the intervention, to get their perspectives. Finally, purposive sampling will be used to facilitate inclusion of women with experience of prior miscarriage from both the control and EUC groups to understand its effects on intervention experience and psychological distress, perceptions of health, and social support in the current pregnancy.

Recruitment for in-depth interviews will include variation across years of schooling (≤5 years vs. ≥5 years) and gravidity/parity (1st baby vs. ≥1 live child), and format in which they received the intervention (all in person, versus those who received some or all sessions over the phone after the COVID-19 precautions began). Per COVID-19 precautions, enrollment will entail the study coordinator calling participants, obtaining verbal consent, and arranging a date and time for the interview. Contact information will then be provided to research assistants responsible for calling participants at the agreed time and the interview will be conducted by phone. To better understand how COVID-19 is affecting our

participants (e.g. to improve our intervention regarding this issue) we have also included some questions on this topic in our interview guide. If women have a lot to say and are tired or it is more convenient for them to do the interview in two telephone calls (one regarding questions on implementation of the intervention and the other on COVID-19) we will offer them to option to participate in two shorter interviews rather than one long one.

For the secondary biological study, we will be examining features of immune and endocrine system alteration in women enrolled in this trial to determine 1) whether there is a pattern of immune dysregulation common to women with antenatal anxiety 2) whether our intervention alters that pattern 3) whether immune dysregulation is related to dysregulation of allopregnanolone and 4) whether these biological mechanisms are mediators or moderators of the success of the intervention in reducing poor birth outcomes. We plan to recruit 300 pregnant women in three groups: 100 will from the intervention group, 100 will be from the enhanced usual care (EUC) group, and 100 will be healthy controls (pregnant women who have scored <8 on both anxiety and depression subscales of the HADS). Participants in the biological study will have their blood drawn at all four study visits; blood will be frozen as plasma at -80 and will be shipped to Johns Hopkins for immune and endocrine analyses.

B. Provide a sample size and a justification as to how you arrived at that number. If you use screening procedures to arrive at a final sample a table may be helpful.

In our study, the unit of randomization is an individual woman, with an equal number of women randomized to the intervention and control groups. We assume an outcome prevalence of CMDs (postnatal depression episode and anxiety) at 30%, which is conservative given that most estimates of prenatal depression in Pakistan are higher than this. (16, 17, 91, 129) While we observed a 50% reduction in postnatal depressive symptoms when evaluating our prior CBT intervention (which was initiated late in pregnancy), we desire 85% power to detect reductions in CMDs as low as 30% (86, 130, 131) , requiring 840 pregnant women (420 in each arm). Anticipating 30% attrition post enrollment, we will enroll 600 women per group in this study, for a total of 1200 women. This sample size of 420 outcomes per group provides ample power to detect important reductions in SGA, which we currently estimate to occur in approximately 47% of births. For example, we will have 90% and 80% power to detect reductions of 23.7% and 20.2%, respectively.

Sample size considerations for the qualitative process evaluation/COVID-questions will be based on a target number of up to 80 women sampled across different characteristics, or until saturation is achieved. We will sample up to 45 women from the intervention group and 25 women from the EUC group and another 10 who dropped out of the intervention. As described (See under Study Design above), these women will be purposively sampled to achieve a wide range of variation (or maximum variation) on various dimensions of interest. To triangulate and learn from multiple perspectives, we will also hold 2 focus group discussions (FGDs) with the HMHB therapists and assessors/screeners involved in delivery, assessments, or coordination of the intervention to ask them about their perspective on the same issues. Topics of interest for sub-group analyses include the effects of transitioning from in-person to by-phone format during the COVID pandemic, distress related to COVID-19, and the effects of prior miscarriage on current pregnancy and intervention experience.

For the secondary biological study, a sample size of 60 subjects in each group, women with anxiety (with and without intervention) and healthy controls, will give us at least 80% power to detect a difference in means of log-transformed cytokines across groups with an effect size of 0.3 to 0.5. This calculation assumes four repeated measurements with exchangeable covariance structure, a correlation of 0.6 and alpha level = 0.05. The smallest observed effect size for CCL3 between anxious and non-anxious women in the preliminary data of 51 women was 0.3 in 1nd trimester to 0.5 in the 2nd trimester (Cohen's D from 0.3 to 0.5). Sample size calculations were performed using the PASS Sample Size Software program.(34) Prior studies in our clinic have an attrition rate of up to 20%, but because the attrition rate for this type of study in Pakistan is unknown we will increase our sample size to account for higher attrition (up to 40%). We will therefore enroll 300 women to yield an ultimate sample size of at least 180.

IV. Participants:

Describe the study participants and the population from which they will be drawn. Specify the inclusion and exclusion criteria. If you plan to include children, note their ages and whether you will include children in foster care. Note if the participants are particularly vulnerable in terms of cognitive limitations, education, legal migration status, incarceration, poverty, or some combination of factors.

Pregnant women attending the outpatient Obstetrics Department of HFH for antenatal care will be approached to determine interest in screening for possible eligibility and participation in the study. Women expressing interest will be asked to provide **consent for screening**, because our screening procedures include a formal assessment using the Hospital and Anxiety Depression Scale (HADS) (see inclusion criteria #6) and the depression component of the Structured Clinical Interview for DSM-5 (SCID) (see exclusion criteria #1). Those providing consent to be screened, will be assessed for eligibility to the intervention and enhanced usual care groups using the below inclusion and exclusion criteria:

- **Inclusion Criteria:**
  1. ability to understand Urdu
  2. ≤22 weeks' gestation
  3. age ≥18 years
  4. residence ≤20 km of Holy Family Hospital
  5. intent to reside in the study areas until the completion of the study
  6. score ≥8 on the HADS anxiety

- **Exclusion Criteria:**
  1. Current major a depressive episode (MDE on SCID) or life-threatening health conditions including e.g. active severe depression or suicidal ideation
  2. Self-reported past or current significant learning disability
  3. Self-reported past or current psychiatric disorder (e.g. bipolar disorder or schizophrenia) or psychiatric care (e.g. current use of anxiolytic drug and/or other psychotropic drug)
  4. medical disorders or severe maternal morbidity that require inpatient management that would preclude participation (e.g. eclampsia, pre-eclampsia, and antepartum hemorrhage)
  5. ICU admission (indicated by diagnosis not admitted only for assessment)

For the healthy control group, unique to the biological substudy, inclusion and exclusion criteria will be as above, except that participants must score <8 on the HADS anxiety.

NOTE: If you are recruiting participants or receiving, accessing, or using data from a U.S. health care provider, HIPAA review is likely to be required. If you plan to bring identifiable health information from a foreign country to a U.S. covered entity (e.g., lab at the Hopkins SOM), HIPAA may be triggered. Check "yes" to the HIPAA question in the PHIRST application.

V. Study Procedures:

In this section, provide details of your procedures, particularly as they relate to human subjects. If this is a multi-center study, make the role of JHSPH clear. If the JHSPH will serve as **data coordinating center**, indicate in the sections below which procedures JHSPH will not be performing. Additional information regarding data coordinating centers is requested in a later section. If your study will develop in phases, address each item below by phase.

A. Recruitment Process:

1. Describe how you will identify, approach, and inform potential participants about your study. Include details about who will perform these activities and what their qualifications are.

   Recruitment for Screening:

Pregnant women will be recruited from the outpatient Obstetrics Department of HFH in Rawalpindi, Pakistan. A study poster containing information about the study will be displayed in the waiting area of the Obstetrics Department. The study poster will contain information about the HMHB trial and eligibility criteria for participation in the study (to solicit interest from literate women in the waiting area). As women check in to the obstetrics department, our research staff will be stationed with the hospital administrative staff. Our main recruitment strategy will involve female members of the assessment team based in the outpatient department who will establish minimum eligibility (based on inclusion criteria #1-5 in Section IV 'Participants' above: age>18, weeks of pregnancy ≤22, ability to understand Urdu, residence ≤ 20 km from HFH, and intention to remain there until the after delivery.) For pregnant women who self-report meeting these criteria (or that we have not already identified as not eligible based on their antenatal hospital record), they will describe and explain the 'HMHB study' to them and their families while visiting the obstetrics department and invite them to be screened for eligibility. Information will be provided in Urdu before any women are asked to provide written informed consent for the screening.

For more details, please see the sections below for a detailed description and the 'Screening Schema HMHB' uploaded in Miscellaneous documents.

COVID-19 Symptoms Screening

The research staff who will interact with study participants, such as for the aforementioned recruitment and screening procedures, will be required to check themselves for COVID-19 symptoms before coming to work, staying home and notifying their supervisor if experiencing symptoms, and self-isolating for at least 14 days after unprotected exposure to a known or suspected case of COVID-19. Study staff who report COVID-19 symptoms from home or are found to have symptoms upon screening at the study site will be referred for COVID-19 testing and care as well as given instructions for self-isolation at home while waiting for COVID-19 testing results and/or completion of 14 days of isolation.

Participants will be screened for symptoms of COVID-19 prior to engaging in any further recruitment, intervention, or data collection activities. Patients who screen positive during triage, to be carried out prior to allowing further entry into areas where research activities are being conducted, will be provided information about referral to testing and/or treatment and self-isolation.

HMHB study staff as well as Holy Family Hospital authorities are adhering to guidelines provided by the Pakistan Ministry of National Health Services Regulations and Coordination as well as the local provincial department of health and ensuring the following workflow measures are taken at the antenatal department:

- Allowing a limited number of women into clinical areas from the entrance gate to ensure patients can feasibly maintain physical distancing
- Not permitting family or attendants to attend with pregnant women in the clinical waiting areas
- Encouraging women to sit with an empty seat between them to maintain social distancing
- Having doctors/study staff screen all individuals in the clinic and in waiting areas by directly inquiring about fever, respiratory problems, and symptoms of COVID-19.
- Recording forehead/temporal scan temperature for all participants who enter research rooms and further screening before subsequent recruitment
- Encouraging use of face coverings and providing face masks to participants prior to engagement in study recruitment or data collection activities

2. Address any privacy issues associated with recruitment. If recruitment itself may put potential participants at risk (if study topic is sensitive, or study population may be stigmatized), explain how you will minimize these risks.

When approaching women to initially introduce the HMHB screening process, we will refer to the study as a study for "mothers-to-be", and to the intervention as one that will promote "maternal child well-being". In addition, we will prioritize the use of the term "stress" and use the term "anxiety" only when necessary. These efforts to use broad language will allow us to avoid stigmatizing terms while still being informative. Women will be interviewed in a quiet area that is separated off in order to ensure privacy.

B. **Consent Process**:

1. Describe the following details about obtaining informed consent from study participants. If a screening process precedes study enrollment, also describe the consent for screening.

   1. Who will obtain informed consent, and their qualifications:

Consent for Screening

A member of the Assessment Team based in the outpatient department will seek consent for eligibility assessment from interested women. The assessment team will explain the screening procedures and eligibility criteria for participation using the consent form in Urdu. If the woman is interested in being assessed (i.e. screened) for eligibility, the screening consent form (See Screening Consent Form 001) will either be provided to the woman (if literate) or, in case of an illiterate woman, the assessment team will read out aloud the Screening Consent Form and clarify any questions the woman may have. In case the woman cannot sign (e.g., due to illiteracy), provision of witnessed consent will be used. This procedure, as alternatives to written informed consent, is routine and culturally acceptable in Pakistan. In case of refusal, the assessment team will maintain a record of the number who declined to participate in the screening. We will gather basic demographic information from the medical record to compare the characteristics of women who consent/do not consent for participation in the study. After obtaining screening informed consent, these women will be assessed for eligibility by the assessment team. Please refer to our Appendix (in Miscellaneous Documents 'Screening Schema HMHB)' for a step by step process.

Screening Procedures:

As described briefly above, we will first approach all women to establish if they are ≥ 18 years old, reside within ≤20 km of Holy Family Hospital, intend to reside in the study areas until the study is complete, and understand Urdu to the HMHB. If they fulfill these demographic criteria, we will invite them to be screened in a private area about other exclusion criteria (e.g. their psychiatric history, history of psychiatric medications and history of a learning disabilities (See 100 Eligibility Screening Master Form, in Surveys/Instruments/Questionnaires in the Miscellaneous Section). If they are not excluded on this basis, these pregnant women will be further screened for having mild to high levels of anxiety on the HADS score ≥8 for anxiety by the research team member. As one of our exclusion criteria is a diagnosis of depression, the Structured Clinical Interview DSM disorders (SCID) module for Depression will also be used as a screening tool to rule out women with this diagnosis among those with a HADS score ≥8 for depression.

Consent for Study Participation: Women who ultimately screen eligible, will then be invited to participate in the main study. The staff person will indicate that based on the results of the screening the woman is eligible to participate, and she will give the pregnant woman a copy of the main study consent form (See 002 - Consent for Study Participation) and will go over the consent form with the woman, answering any questions she may have about the study. The woman will be approached first if possible and will be able to ask any questions, and/or take time to make a decision about participating. Although we are not asking husbands or other family members for consent, if there are family members present and the woman wishes for them to be present during the consent process we will comply with her wishes. We will describe and explain the study to both the woman and any accompanying family/friends. Women can decide at this point of contact to participate, or they may choose to take some time to make their decision (up to 14 days). If the latter option (i.e. delayed decision), our staff member will request a phone number to follow up with the

woman to determine if/when she has made a decision so that a separate baseline visit can be scheduled. (This will also give her the opportunity to think about it and consult with family members who are not present if she so desires before she consents.) If the first option is taken (i.e. immediate decision to participate), the staff member will conduct the baseline assessment on the same day. In both cases, the consent form with signature indicating consent to the procedures will be required before moving to baseline visit procedures.

Who will conduct Screening Consent, Screening Procedures, and Consent for Study Participation: HMHB members of the Assessment Team who will also be based in the hospital will ask for the potential participants' consent. These Assessment Team members will be bachelor degree graduates in social sciences, fluent in Urdu with at least one year of experience in research. They will receive training on consenting procedures and will follow standard protocol of approaching participants and providing information. As part of the consent (002 – Consent for Study Participation), the research Assessment Team will explicitly explain that the decision to participate (or to not participate) in the study will have no consequences on the usual care received by the participants and that they can withdraw their consent for participation in the study at any time without their usual care being affected.

2. How, where, and when the consent discussion(s) will occur:

Consent for Screening and Consent for Study Participation procedures/discussion will take place in a separate room or outdoor space in the presence of a nurse/ relative as a witness while taking COVID precautions. For those eligible and interested in participating, written consent will be obtained. If participant cannot read, it will be read out loud to them.

The process you will use to determine whether a potential participant meets eligibility criteria:
See subsection above title "Screening Procedures" in Section V.B.1 for full details on the screening procedures.

3. Whether you will obtain a signature from the participant or will use an oral consent process:

For both screening consent and study consent, we will obtain a signature to indicate consent, except in the case of illiterate women for whom we will obtain witnessed consent. These procedures as alternatives to written informed consent are routine and culturally acceptable in Pakistan.

4. Whether you will obtain a legally authorized representative's signature for adults lacking capacity:

Adults who are lacking capacity (e.g. have a significant learning disability, severe depression, psychosis, etc.) will not be included in the study.

5. If children are included in the study, if and how you will obtain assent from them:

N/A

6. If children are included in the study, how you will obtain permission for them to participate from their parent, legal guardian, or other legal authority (if child is in foster care or under government supervision):

N/A

7. If you are seeking a waiver of informed consent or assent, the justification for this request:

N/A

8. Whether you will include a witness to the consent process and why:

In the case that someone is unable to sign witnessed consent will be obtained, with a nurse, other hospital staff or a relative of the patient serving as a witness. This is a standard protocol for our Pakistani research team as a part of good clinical practice and transparency, i.e. to assure that someone impartial without a conflict of interest (unrelated to the study) has verified that the person in fact did willfully consent.

9. If the language is unwritten, explain how you will communicate accurate information to potential participants and whether you will use props or audio materials:

N/A

2. Identify the countries where the research will take place, and the languages that will be used for the consent process.

Country	Consent Document(s) (Adult Consent, Parental Permission, Youth Assent, etc.)	Languages
Pakistan	Consent for Screening (Adults) Consent for Study Participation (Adults)	Urdu

1. **Study Implementation**:

1. Describe the procedures that participants will undergo. If complex, insert a table below to help the reviewer navigate.

Recruitment / Consent / Randomization: Pregnant women coming for their initial prenatal visit will be screened for eligibility; this includes being "at risk" for anxiety on the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS) or having moderate or high levels of anxiety (i.e. a cutoff of ≥ score of 8). Informed consent will be obtained from eligible women and those agreeing to participate will be individually randomized to either the HMHB intervention or enhanced usual care (the control). A randomization sequence with varying block size (i.e. randomly permuted sizes of 4, 6, 8, and 10) will be generated by an independent researcher who is located off-site (Institute of Psychiatry, Rawalpindi, Pakistan) and is not involved in running of the study. The individual allocations will be provided to the study staff in opaque sequentially-numbered envelopes and utilized sequentially at the time of enrollment of each participant. Each woman randomized into the HMHB group will be assigned to a HMHB non-specialist provider to introduce them to the program.

Intervention Group: Women allocated to this group will receive the HMHB intervention. The content of HMHB will be based on 1) formative research (completed last year), 2) prior cognitive behavior therapy-based approaches to

intervention delivery in LMICs,(35-37) and 3) lessons learned from the implementation of THP.(38) The intervention will include a woman-centered focus. In the sessions, we will employ core principles of CBT with a focus on anxiety.(36) HMHB modules focus on the mother's psychosocial well-being, delivery/birth preparedness, relationship building and enhancing psychosocial support of significant others, and other salient issues identified in the formative phase. Specifically, CBT techniques from THP that have been useful for anxiety include structured sessions, psycho-education, active participation, thought challenging, problem solving, behavior activation, and relaxation techniques. These common techniques are also indicated in the method called the Common Elements Treatment Approach (CETA), developed specifically for use with non-specialist providers in LMICs.(39) Pregnant women will be offered 6 core weekly sessions and between 2 to 6 booster sessions depending on gestational age at enrollment. The final core session will be in the 3rd trimester of pregnancy. Our intervention has been fully developed, culturally adapted and tailored to a low-literacy population(40) during the formative research phase (year 1). Fidelity will be measured using indicators for both quality (via role play during supervision sessions) and quantity (e.g. number of sessions, session attendance, treatment failures). We will also record a sub-sample of at least 10% of consenting women's sessions to evaluate them using the ENACT scoring system for global training and supervision in mental health.(41) To address stigma,(42) HMHB will be presented as a 'mother to be' program rather than being specifically targeted for 'maternal mental health.' Family members will be invited to three sessions, to promote their support.
The intervention (i.e. the HMHB sessions) will be provided by non-specialist providers, who will receive simplified training followed by regular supervision.(37) These trainers will have a university degree in the social sciences, at least one year of relevant work experience and knowledge of the local language, but no prior experience in mental healthcare delivery. During year one of the funded grant, they have received a six-day training. Further training will include practice in the field and regular group supervision. The data collection team ('assessors') and non-specialist providers ('trainers') will be continually monitored. During the training period, data collectors will be assessed for interrater reliability (IRR).

Enhanced Usual Care (EUC) Control Group: Women allocated to the control condition will receive EUC. The WHO recommends eight antenatal visits for a positive pregnancy experience(43) which we will be the target number of visits for EUC participants (depending on their gestational week). Visits will involve evaluating health status, discussing any concerns, and performing routine exams consistent with stage of pregnancy. For EUC medical staff at the hospital will receive additional mental health training. Transportation will also be provided or facilitated for participants to assist with attending appointments and up to two ultrasounds will be paid for by the study.

Healthy Controls (HC): For the purpose of this revised application we will add a 2nd control group of 100 women who have low or no anxiety or depressive symptoms (<8 on both the anxiety and depression sub-sections of the HADS). This will allow us to compare biological processes in a group of anxious women with the intervention, a group of anxious women without the intervention and compare them to these healthy controls (non-anxious or depressed, without the intervention).

All three Groups: All medical staff will be trained on the WHO Mental Health Gap Action Programme (mhGAP) curriculum on management and intervention for common mental disorders. Transportation will be reimbursed or provided for women in all three study arms and participants will be offered 400 rupees ($4) or a mobile phone "top up" voucher of 400 rupees for participation. Participants will also be reimbursed the cost of ultrasounds indicated by their medical team at Holy Family Hospital.

For only women in this 'revised' biological R01 study: All 300 women (intervention, EUC, and healthy control) in the supplement grant application will receive baby gifts (up to $10) at the completion of the study as a thank you.

During our preliminary formative research (IRB #7678) during the last year, we conducted in-depth interviews with expectant mothers experiencing anxiety (n=19) and health professionals (n=10) to identify risk factors, means of expressing anxiety, current coping strategies, and the acceptability and feasibility of a facility-based intervention targeting anxiety among expectant women. The content and strategies employed by HMHB are informed by the findings of our

formative study and other relevant literature. Evidence-based strategies for managing anxiety and behavior activation are used in HMHB. Psychosocial risk factors of anxiety such as adverse life events, interpersonal problems, lack of social support, pregnancy complications, and fear of labor are addressed in the intervention.

The dosage of the HMHB is informed by evidence from the literature. The United Kingdom National Institute for Health and Care Excellence (NICE) guidelines recommends between five and seven individual CBT-based sessions for anxiety management. Recent systematic reviews of CBT-based perinatal anxiety interventions indicate that 6 to 12 sessions were effective in reducing symptoms of perinatal anxiety.(99, 100) The HMHB intervention consists of six core sessions and between two and six booster sessions. Core sessions focus on (1) psycho-education and stress management, (2) personal wellbeing, (3) social support, (4) mother-infant bonding during pregnancy, (5) relapse prevention, and (6) preparation for the baby and early postnatal period. The first five core sessions will be delivered weekly to ensure that expectant women receive maximum dosage as early in their pregnancy as possible. The sixth session will be delivered later, in the third trimester. Booster sessions will be delivered during the expectant women's routine antenatal visits to the hospital between the fifth and sixth core sessions. Based on at what gestational week a woman is recruited into the study, each woman will receive between two and six booster sessions. Sessions will last between 45 minutes and an hour. Family member/s will be invited to attend the first, third, and sixth core sessions

Table 1 indicates the active ingredient and timing of each session for the intervention arm.

Table 1: Description of intervention Sessions

Sessions	Active ingredient	Timing of session delivery	Recipients
Session 1: Psycho-education and Stress Management	Psycho-education (Knowledge about anxiety disorders and stress management skills)	Weekly	All participants recruited into the intervention arm and their family members
Session 2: Personal Wellbeing	Thought challenging and behavior activation (Strategies for improving overall wellbeing, including diet, rest, relaxation, sleep, and managing common complaints during pregnancy)	Weekly	All participants recruited into the intervention arm
Session 3: Social Support	Thought challenging and behavior activation (Strategies for improving interpersonal relationship and social support).	Weekly	All participants recruited into the intervention arm and their family members
Session 4: Bonding with the infant during pregnancy	Thought challenging and behavior activation (Strategies for improving bonding with the infant during pregnancy). Addressing fear of child-birth (knowledge and planning of safe delivery).	Weekly	All participants recruited into the intervention arm

Session 5: Staying Well	Relapse prevention (problem management strategies to prevent relapse).	Weekly	All participants recruited into the intervention arm
Booster sessions (2–6 depending on time of enrollment)	Behavior activation and problem management skills	Booster sessions will be coordinated with the recipients' routine antenatal visits.	All participants recruited into the intervention arm
Session 6: Preparing for the baby and early postnatal period	Addressing fear of child-birth (strategies for planning for baby's arrival). Psycho-education (coping with early post pregnancy challenges).	Late pregnancy	All participants recruited into the intervention arm and their family members.

Control arm:

Women randomized to the control group will receive usual care. The WHO recommends eight antenatal visits to optimize a positive pregnancy experience (103) which we will be the target number of visits for study participants in the control group (depending on their gestational week). These visits will involve evaluating health status, discussing any concerns, and performing routine exams consistent with stage of pregnancy. Usual care will be slightly enhanced by medical staff at the hospital receiving additional training in mental health treatment to counsel participants. Please refer to Table 3 for details about the content and schedule of usual care.

Table 2: Description of Usual Care*

Visit	Content	Timing of visits as per WHO recommendation	Recipients
Visit 1:	Assessment for anemia; dietary counselling about healthy eating and keeping physically active during pregnancy; folic acid supplements; counseling for common physiological symptoms; emphasizing eight antenatal care visits	Following recruitment	All participants recruited into the study (intervention and control arm)
Visit 2:	Assessment for anemia; dietary counselling about healthy eating and keeping physically active during pregnancy; Iron and folic acid supplements; vaccination; counseling for common physiological symptoms; emphasizing eight antenatal care visits	Second trimester	All participants recruited into the study (intervention and control arm)

Visit 3:	Assessment for anemia; dietary counselling about healthy eating and keeping physically active during pregnancy; Iron and folic acid supplements; vaccination; counseling for common physiological symptoms; emphasizing eight antenatal care visits	Second trimester	All participants recruited into the study (intervention and control arm)
Visit 4:	Assessment for anemia; dietary counselling about healthy eating and keeping physically active during pregnancy; Iron and folic acid supplements; counseling for common physiological symptoms; emphasizing eight antenatal care visits	Third trimester	All participants recruited into the study (intervention and control arm)
Visit 5:	Assessment for anemia; dietary counselling about healthy eating and keeping physically active during pregnancy; Iron and folic acid supplements; counseling for common physiological symptoms; emphasizing eight antenatal care visits	Third trimester	All participants recruited into the study (intervention and control arm)
Visit 6	Assessment for anemia; dietary counselling about healthy eating and keeping physically active during pregnancy; Iron and folic acid supplements; counseling for common physiological symptoms; emphasizing eight antenatal care visits	Third trimester	All participants recruited into the study (intervention and control arm)
Visit 7	Assessment for anemia; dietary counselling about healthy eating and keeping physically active during pregnancy; Iron and folic acid supplements; vaccination; counseling for common physiological symptoms; emphasizing eight antenatal care visits	Third trimester	All participants recruited into the study (intervention and control arm)
Visit 8	Assessment for anemia; dietary counselling about healthy eating and keeping physically active during pregnancy; Iron and folic acid supplements; vaccination; counseling for common physiological symptoms	Third trimester	All participants recruited into the study (intervention and control arm)

*Women will also get ultrasound scans as is medically indicated during their prenatal visits. There is typically one in the 2nd and another in the 3rd trimester, but these (and any other additional scans) will occur at the visit/s that the doctor indicates.

In addition to the HMHB information/counseling that is provided to individuals in the intervention arm (Table 2) and the routine information/care provided to those in both the intervention and control arm (Table 3), study procedures also include four data collection timepoints (Baseline, Late Pregnancy, Delivery/Birth, and 6 weeks Post Partum. Procedures that participants will undergo in each of these visits are equivalent between the two study arms, and are summarized below both in brief textual narrative, and in Table 4.

Baseline

Data will be collected on psychosocial factors (social support, quality of marital relationship, empowerment and functional disability, behavioral activation). We will also collect data on other socio-demographic variables including maternal age (years), maternal weight (kg), socio-economic assets (adapted from the Pakistan DHS),(44) marital status (married, single, widowed), education (years of formal education completed), and literacy (literate, semi-literate, not literate) and medically-related variables including gestational age of current pregnancy, number of pregnancies, history of SGA, LBW, PTB, stillbirth, and any complications in previous pregnancies/births. We will also collect data on current medications and current medical status, i.e. gestational diabetes, hypertension, anemia, mid-upper-arm circumference, smoking, substance abuse, and medication use for depression (though we expect these last three to be uncommon). An intimate partner violence (IPV) screening question will be administered so that referrals can be made if any women experience IPV. Women in the biological sub-study will also have their blood drawn (up to 20 mL) by a study clinician or a research assistant trained in phlebotomy. Each participant will be scheduled as close to possible to the same time of day during the morning hours for all four blood draws (as blood is drawn in HFH between 8:00am and 1:00 pm), allowing us to control for diurnal variation in cytokine levels. Blood will be collected in sodium-heparin tubes for immune cell preparation. Blood will be centrifuged within 8 hours of collection by low-density gradient centrifugation via a Z326 High Performance Centrifuge . Plasma will immediately be frozen in cryovials at -80 C in a ThermoScientific Revco RLE Ultra-Low Lab Freezer and will be stored there until it is shipped to Baltimore for analysis at the end of the trial.

At 24 weeks:

Women participating in the biological substudy will have a blood draw (using same techniques described above under 'baseline visit') and will complete the HADS at this visit; other women in the main trial will not have a visit at 24 weeks.

At 3rd trimester

Data will be collected about anxiety related to the pregnancy/delivery itself (PES-brief), perceived stress, fetal outcome (SGA in utero from medical records), social support, quality of marital relationships, functional disability and cost of service utilization and behavioral activation. An intimate partner violence (IPV) screening question will be administered so that referrals can be made if any women experience IPV. Women in the biological substudy will also have a blood draw (using same techniques described above under 'baseline visit').

At birth:

Data will be collected on SGA, low birthweight and preterm birth. To evaluate IUGR at birth, we will classify small-for-gestational age (SGA) by using birthweight, gestational age, and sex of the infant, from the birth using the recently developed Intergrowth (45) standards (http://www.intergrowth21.org.uk/). Data will also be collected regarding

breastfeeding from mothers, and from the medical records regarding pregnancy outcomes and any medical conditions (e.g. pregnancy complications).

Table 3: Birth outcomes and their definitions

Endpoints	Measurement	Use and scoring
Intrauterine growth restriction (IUGR) at birth	At birth: Small-for-gestational age (SGA) will be used as a proxy for IUGR.	Use: Secondary outcome Scored: weight <10th% for gestational age
Preterm birth (PTB)	Weeks of gestation at birth	Use: secondary outcome Scored: <37 weeks' gestation
Low birthweight (LBW)	Weight in grams at birth	Use: secondary outcome Scored: ≤2500 grams

We will also gather data from medical records on ultrasounds in the 2nd and 3rd trimester, in order to have the possibility of looking at fetal growth over time (measured then and at birth).

Follow-up (6 weeks postpartum):

The primary endpoint will be assessed at six weeks postpartum (with flexibility for -1 week and +4 week window if needed because of scheduling reasons). Women returning for their routine 6-week postpartum visit will be asked to undergo a final follow-up assessment conducted by the Assessment Team, who will be masked to the allocation status of trial participants. Women in the biological substudy will also have a blood draw (using same techniques described above under 'baseline visit'). We will also administer the *Ages & Stages Questionnaire, Third Edition (ASQ-3)* to the infants of all participants in the trial to assess infant neurobehavioral functioning.

For the detailed description of the outcomes and time points, see **Table 4** below.

In the chart below, data collection procedures that are specific to the substudy are marked as Os in the chart instead of as Xs.

Table 4: Schedule of study assessment activities

	Screening	Baseline *	2nd trimester	3rd trimester**	Birth	6 weeks postpartum **
	Time 1	Time 2	Time 3	Time 4	Time 5	Time 6
Informed Consent	X	X				
Eligibility assessment						
Screening step 1 (age, residence, stage of pregnancy, language)	X					
Screening Step 2 (medical exclusions)	X					
Screening Step 3 (HADS anxiety inclusion)	X					
Screening Step 4 (SCID MDE exclusion)	X					
Assessments						
Socio-demographic questions		X				
PSS-10 (stress)				X		X
PES-Brief (pregnancy anxiety)		X		X		
PHQ-9 (depressive symptoms)						X
HADS (anxiety symptoms)		X	O	O		X
HADS (symptoms of depression)		X	O	O		X
MDE diagnosis (from SCID)		X				X
MSPSS (social support)		X		X		X
MRQ (relationships)		X		X		X
Empowerment		X				X
WHO-DAS (disability)		X		X		X
DHS IPV items (violence)						X
IPV Screening Question		X		X		(in the DHS module)
PAAS (behavioral activation)		X		X		X
Breastfeeding					X	X
Parenting self-efficacy						X
PBQ (bonding)						X
MIRI (maternal responsiveness)						X
MSEQ (maternal self-efficacy)						X
Anthropometry§§						X
Economic Data						
CSRI				X		X
Blood Draw (for biology aims)		O	O	O		O
Ages & Stages Questoinnaire, Third Edition (ASQ-3)						O
From medical records						
Fetal outcome: *SGA in utero**				X		
Pregnancy conditions:				X		
Birth outcomes: *SGA, PTB, LBW*					X	
Medications		X		X		X
Pregnancy conditions: medical status in pregnancy (e.g. pre-eclampsia, gestational diabetes)		X		X	X	X
Adverse event review	AT ALL TIMES					

*Baseline assessment may be the same day or up to two weeks after screening.

Note: Full descriptions of the assessment tools are given in section 8.2.3.

**Assessments will be somewhat flexible; the 6-week postpartum visit can be done a week early and up to three weeks after the 6 week mark (if scheduling issues preclude collecting data exactly at the desired time)

§This screener will be administered in order to be able to refer women with IPV to counseling, since it is considered an adverse event.

§§Anthropometry will be measured either our team or a healthcare provider at the 6 week postpartum visit.

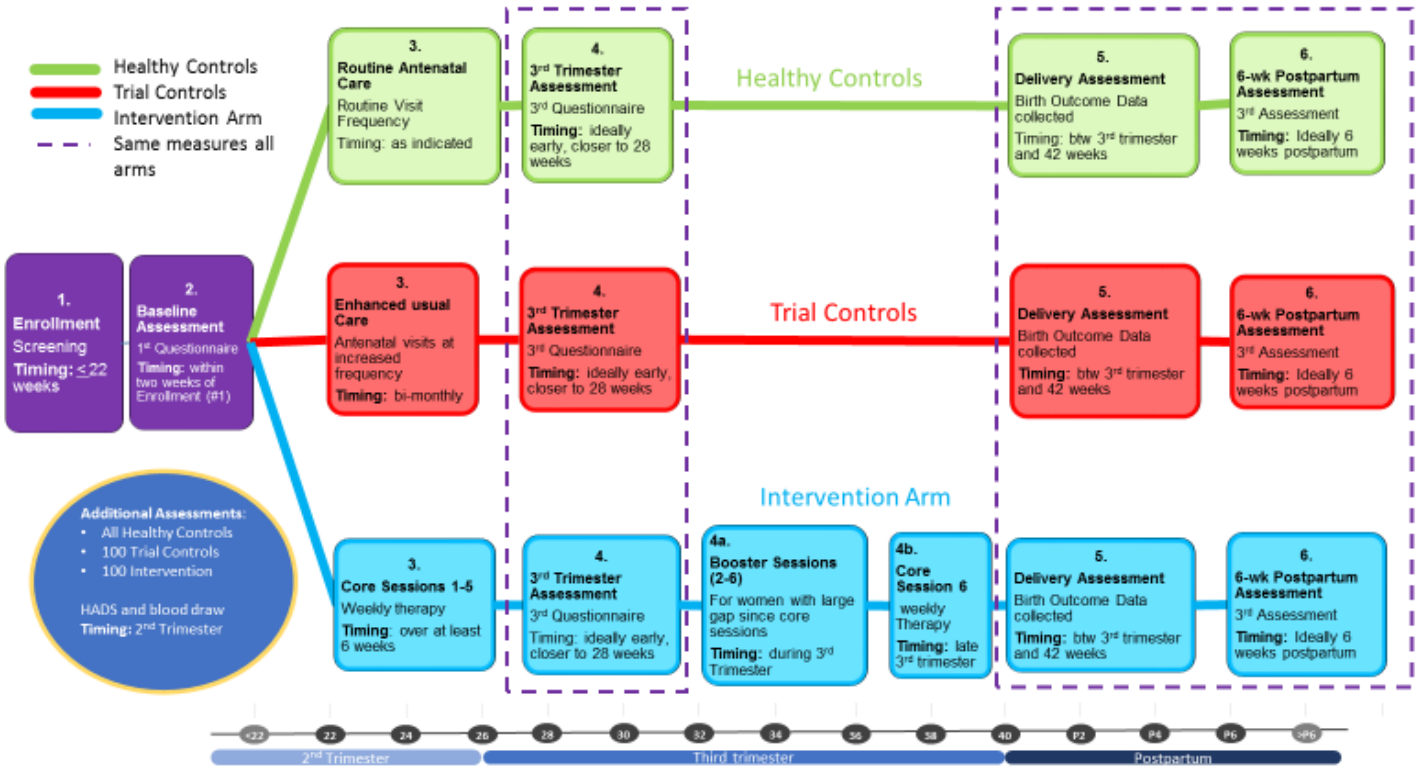
2. Describe the number and type of study visits and/or contacts between the study team and the participant, how long they will last, and where/how they will take place.

For the assessments there will be a screening visit at the time of enrollment, visit at baseline (either at the same time if the woman is ready to enrol or within 2 weeks afterwards if she would like more time to think about it), in late pregnancy, at delivery, and at 6 weeks postpartum. See above for assessments that will be done at each visit. We expect baseline and the 6 week postpartum visits to last between 1 to 1.5 hours. We expect the 3rd trimester visit to be shorter, around 45 minutes. We expect the birth visit to only entail 5 minutes of data collection with the women, while the rest will be gathered from medical records.

For women randomized to the intervention, there will be 6 core intervention sessions and up 2-6 booster sessions (depending on the time of enrolment). The first five core sessions will be delivered weekly as early in the pregnancy as possible, then the booster sessions will occur, with one final core session (Core Session 6) in the 3rd trimester. Booster sessions will be scheduled on a case by case basis, depending on the recruitment time of the pregnant mother. Please see Table 2 above for an outline of session content.

For women in the biological substudy, there will be an additional visit at 24 weeks gestation for a blood draw and HADS administration. See the Figure below for a timeline of study visits.

Figure: Timeline for participants in the intervention and control arms of the main trial



All assessments and will be in the hospital, and we will attempt to pair them with her regular prenatal and postnatal medical visits when possible.

3. Describe the expected duration of the study from the perspective of the individual participant and duration overall.

Sessions will last between 45 minutes and an hour, and data collection will extend from the time of enrolment in early pregnancy (≤22 weeks gestation) until the 6 week postpartum-end-point assessment.

Those who are randomized to the intervention arm will additionally experience the intervention. Please see Tables 1 and 2 for an outline of sessions for intervention and control participants, respectively.

4. Provide a brief data analysis plan and a description of variables to be derived.

Analysis of Primary Efficacy Endpoint(s)

The primary outcome of the study is the prevalence of cases of CMDs (GAD and MDE) in both study arms. Diagnosed cases of both GAD and MDE will be assessed with the Structured Clinical Interview for DSM Disorders (SCID).

The intervention group (enrolled after being screened for subclinical or clinical levels of anxiety) will be compared with non-intervention controls (selected on the same criteria) to examine the effects of the intervention on development of CMDs. The primary analysis will involve comparing pre- to post- changes in cases of the mothers randomly assigned to the two conditions using Fisher's exact test. Primary analyses will be non-parametric tests, however sensitivity analyses will use parametric models such as linear and logistic regression to control for baseline values of the mothers' characteristics (132). Other sensitivity analyses may evaluate whether there was more of an effect among women who got the full intervention. Variable transformations (such as square root or log) will be utilized as appropriate to meet the model assumptions.

Analysis of Secondary Efficacy Endpoint(s)

We will secondarily compare the intervention and control groups in terms of changes in CMD symptom scores, by measuring depressive symptoms with the 9-item Patient Health questionnaire (PHQ-9) and the HADS anxiety questionnaires. Other outcomes of interest, but not primary targets, include birth outcomes (SGA, LBW, and preterm birth), perceived stress (using the Perceived Stress Scale –PSS), pregnancy-related anxiety (using the Pregnancy Experience Scale PES-Brief), maternal functioning (using WHO-DAS), marital relationships (MacArthur Relationship Questionnaire), IPV, women's empowerment, maternal bonding, maternal responsiveness, child growth at 6 weeks postpartum, as well as initiation and exclusivity of breastfeeding (WHO measures). Pregnancy-related symptoms of anxiety (measured with the PES-Brief) will be assessed at baseline and in the 3rd trimester.

For secondary hypotheses, we will estimate the effects of the intervention using birth and follow-up (6 weeks postpartum) measures separately. Primary analyses will be non-parametric tests, however sensitivity analyses will use parametric models such as linear and logistic regression to control for baseline values of the mothers' characteristics (132). Variable transformations (such as square root or log) will be utilized as appropriate to meet the model assumptions. For primary and secondary endpoints, in all regression models the coefficient on the HMHB vs. non-HMHB (control group) indicator variable will be taken as the estimated effect.

Analysis of Variables from Biological Substudy

Statistical Analysis. Oversight for the statistical analyses will be provided by Dr. Gayane Yenokyan of the Johns Hopkins Biostatistics Center. The initial statistical approach will include a descriptive cross-sectional analysis at each time point, both for quality assurance and to attain a better understanding of the distributions of the outcome variables for use in subsequent analyses, including the need for any transformations, followed by the longitudinal analyses. For **Aim 1**, we will assess the associations between cytokine levels as dependent variables and level of anxiety (as measured by the HADS) as the independent variable. The level of anxiety will be considered from the following perspectives: 1) dichotomous (above and below HADS=8) and 2) continuous. In both analyses, we will compare women with anxiety vs. healthy controls and with and without the intervention to evaluate whether there is a positive association between

cytokines and other immune markers with anxiety. In addition, we will perform a comparison of immune markers between women disease/intervention groups adjusted for potential confounders that are differentially distributed by disease group, using multivariable linear regression model at each time point. We will assess whether association between immune marker and anxiety is different by group and by visit. In the longitudinal analyses, we will fit generalized linear mixed effect models to account for within-woman correlation of inflammatory markers.[241] The model will include indicators for visit and group as well as any relevant interaction terms (e.g. group by visit). The models will adjust for baseline severity and other patient characteristics. A random effect for woman will be included as a random intercept. Other, more complex model structures will be explored, such as a model with random slope or non-independent residual correlation structure. These models account for missing at random, i.e. missing data are assume to depend on prior immune marker values and covariates. Standard model checking will be performed and the most parsimonious model will be selected based on the Akaike Information Criterion (AIC).[242]

For **Aim 2,** we will follow the same approach, with ALLO levels as the independent variables and anxiety as the dependent variable. Generalized linear mixed effects models will be fit to the data to model anxiety trajectories while accounting for within-women correlation of these measures. Estimated anxiety trajectories and ALLO levels will be used as candidate independent variables in a logistic regression model of risk of PPD. Cross-validated area under the curve will be used to assess model discrimination between women with and without PPD.

For **Aim 3**, we will assess the associations between ALLO levels and immune markers at different times during pregnancy by disease/intervention group and will fit similar generalized linear mixed effects models described in Aims 1 and 2. These models will first be fit for each immune marker separately and then combined into a multilevel model with crossed random effects that includes with random intercepts for woman and immune marker to "borrow information" across multiple immune markers within the woman.

For **Aim 4**, our analysis will focus on the association of perinatal anxiety and birth outcomes, specifically assessing mediation in both cross-sectional and longitudinal analyses partitioning the total effect of anxiety on birth outcomes as direct and indirect, through change in cytokine and hormone levels.[243]

Missing Data

Adjusted analysis and subgroup analysis will be based on covariates at baseline without non-missing values. Sensitivity analysis will be performed on the covariates with missing values imputed (133). Detailed imputation methods will be described in the statistical analysis plan. All analyses will be detailed in the statistical analysis plan, which will be finalized before un-blinding the study.

Baseline Descriptive Statistics

Regarding quantitative data, we will implement reliability and quality control checks, including randomly selected reliability checks on administration (in real time so corrections can be made, not compromising data quality) and scoring/coding of all measures within one week for completeness and accuracy. All questionnaires completed by trained assessment team members will be reviewed for skipped items or ambiguous answers; assessment team members will be asked to correct any missing or ambiguous entries. Data will be double entered. Data files will be checked with software for discrepancies, flagged and corrected. Although we will attempt to minimize the effects of missing data, some data will likely be missing due to maternal non-response at particular time points. Analyses will be conducted to examine the prevalence and patterns of missing data and methods appropriate for dealing with missing data (such as multiple imputation) will be used. All analyses will use an intent-to-treat (ITT) approach, using all subjects randomly assigned to treatment or control groups. Exploratory analyses will investigate whether effects are larger among mothers who participated in more intervention sessions (estimating complier average causal effects)(136). We will also do preliminary analyses to ensure that the randomization succeeded in creating similar groups at baseline. Baseline variables that are distributed unequally between the intervention and control groups will be adjusted for in the parametric models (below). Finally, to document a data collector effects, we will calculate inter-rater reliability (IRR) during the training period and calculate the Intra-class Correlation Coefficient (ICC) to measure differences between data collectors.

Mediation Analysis

In order to understand the potential mediating effects of stress and social support and women's empowerment in the 3rd trimester (the primary mediators of interest) on CMDs (combined GAD and MDE) at 6 weeks postpartum, we will estimate direct and indirect (i.e. mediated) effects of the intervention using a model-based mediation package by Kosuke Imai (138). At a simple level, these mediation methods can be thought of as estimating a series of regression models, which we will use to test beliefs about the underlying process relating the mediating variables to the outcomes. Because mediation analyses depend heavily on some key identifying assumptions and the specific model forms and variables included in the models, we will do extensive diagnostics and sensitivity checks (e.g., goodness of fit tests, exploring alternative specifications and variables to be included). A benefit of the Imai et al. mediation package is that it has built-in sensitivity analyses to the key assumptions, such as that of sequential ignorability of the mediator (that the mediator values are independent of the potential outcomes, conditional on the treatment and observed covariates). All analyses within this aim will be exploratory given limited power for detecting these interaction effects and difficulties in interpreting mediational effects as causal (139).

Moderator Analysis

To examine potential effect modifiers of the intervention treatment effects on birth outcomes, we will expand the regression models to include a term for the interaction between intervention group status and the potential moderators (exposure to social support, stress levels, marital relationship and empowerment measured at baseline as well as retrospective report of IPV measured at 6 weeks postpartum). This will allow us to examine whether the effects of HMHB differ for mothers (or their children) with varying levels of the potential moderators; analyses will be informed by recommendations in Aiken and West (1991)(140) and Preacher et al. (2006) (141). This aim will be exploratory given limited power for detecting interaction effects.

5. Answer the following **if they are relevant to your study design**:

- If the study has different arms, explain the process for assigning participants (intervention/control, case/control), including the sequence and timing of the assignment.

Study statistician will produce a random sequence of assignments to the study arms. This sequence will be generated using a pseudo random-number generator, and will be constructed using randomly permuted blocks of size 4, 8, 12, and 16. The assignment list will be printed in order, with each step of the sequence separately stored in opaque envelopes and numbered sequentially. When an individual who has been determined as eligible via the screening procedure subsequently provides consent for study participation, the X will pull the next available envelope, opening it, and recording the assignment to intervention or control.

In addition to the participants randomized through the main study, there will be three arms for the biological study. We will choose the first 100 participants each in the intervention and control arms, and will also recruit a group of 100 healthy controls (HADS <8) who will participate only in the biological study.

- If human biospecimens (blood, urine, saliva, etc.) will be collected, provide details about who will collect the specimen, the volume (ml) and frequency of collection, how the specimen will be used, stored, identified, and disposed of when the study is over. If specimens will be collected for use in future research (beyond this study), complete the "Biospecimen Repository" section below.
-

Biological Outcome Variables: Subjects will have their blood drawn (up to 20 ml) at all four visits by a study clinician or a research assistant trained in phlebotomy. Each participant will be scheduled as close to possible to the same time of day during the morning hours for all four blood draws (as blood is drawn in HFH between 8:00am and 1:00 pm), allowing us to control for diurnal variation in cytokine levels. Blood will be collected in sodium-heparin tubes for immune cell preparation. Blood will be centrifuged within 8 hours of collection by low-density gradient centrifugation via a Z326 High Performance Centrifuge. Plasma will immediately be frozen in cryovials at -80 C in a ThermoScientific Revco RLE Ultra-Low Lab Freezer and will be stored there until it is shipped to Baltimore for analysis at the end of the trial.

Shipping of Samples: Plasma samples (approximately 4800 cryovials) will be shipped from Pakistan to Baltimore at the end of the trial for analysis using Federal Express courier services. Blood will stay frozen at a minimum of -20 throughout shipment, using standard cold packs, dry ice, or liquid nitrogen as required by local regulations and the standards of the courier services. Because we will not be able to maintain a tempurature of -80 during shipping, we plan to use multiple shipments (6-8) so that we can initiate analysis immediately upon arrival in Baltimore to avoid freeze-thaw cycles. (Shipping all vials at once will yield a batch too large for the capacity of our laboratory and staff to process at once.) Leftover samples will be refrozen for possible additional future analyses and will be stored in Dr. Osborne's lab at the Women's Mood Disorders Center, Johns Hopkins School of Medicine.

Blood Sample timing: Targets times for sampling blood will be at baseline (between 10 and 22 weeks), during the second trimester (24 weeks ± 2), the third trimester (36 weeks ± 2) and at 6 weeks ± 2 postpartum). All samples will be drawn in the morning (between 8:00 am and 1:00 pm) to minimize differences due to diurnal fluctuations in cytokine levels.

- If genetic/genomic analyses are planned, address whether the data will be contributed to a GWAS or other large dataset. Address returning unanticipated incidental genetic findings to study participants.

N/A

- If clinical or laboratory work will be performed at JHU/JHH, provide the JH Biosafety Registration Number.

BC1512080301 (BSL1) and B1512080101 (BSL2).

- If you will perform investigational or standard diagnostic laboratory tests using human samples or data, clarify whether the tests are validated and/or the lab is certified (for example is CLIA certified in the U.S.). Explain the failure rate and under what circumstances you will repeat a test. For all human testing (biomedical, psychological, educational, etc.), clarify your plans for reporting test results to participants and/or to their families or clinicians. Address returning unanticipated incidental findings to study participants.

Cytokine Analysis. Cytokine analysis will take place in the Becton Dickinson Immune Function Laboratory of the JHBSPH. Plasma cytokines will be measured using the Meso-Scale Discovery (MSD; Gaithersburg, MD) Ultrasensitive Proinflammatory multiplex kit. The MSD multispot array will be run according to the manufacturer's protocol. Calibration curves will be prepared. Plates will be read using the MS2400 imager (MSD). Samples for each case and

matched control will be assayed adjacently, but in random order and in replicate. To determine assay reliability, we will calculate the coefficient of variation (CV%) for each woman's replicates when both have concentrations above the LOD.(46)

Hormone Analysis. All hormone analyses will take place in The Clinical Research Unit Core Laboratory at the Johns Hopkins Bayview Medical Campus. The Core also includes a Sample Processing Laboratory. Directed by Neal Fedarko, PhD, a professor in the Division of Geriatric Medicine and Gerontology, the laboratory offers 87 distinct assays of clinical chemical endpoints and biomarkers to support university research protocols. ALLO will be analyzed with the EIA kit from Arbor Assays LLC Cat 3 KC44-H1. Progesterone will be analyzed with EIA kit from Alpco catalogue # PROHU-E01.

- If your study involves medical, pharmaceutical or other therapeutic intervention, provide the following information:

1. Will the study staff be blind to participant intervention status?

The proposed study is a single-blind, individual randomized clinical trial. The assessment team, trial statistician, and PIs will be masked to allocation status of study participants. To maintain masking during the trial, intervention and assessment teams will not have any interaction during the trial, as they will be placed at separate locations within the Obstetrics Department of HFH. Furthermore, participants will be instructed not to disclose which type of treatment they are receiving to the assessment team. Fidelity of masking will be measured by having assessors guess the trial arm of each participant at the end of follow-up assessment. We hypothesize that assessors will only be able to correctly guess the condition of participants at a chance rate of nearly 50% at follow-up assessments, indicating that masking is maintained.

2. Will participants receive standard care or have current therapy stopped?

Each woman randomized into the HMHB intervention arm will receive the HMHB intervention program plus usual care. Women allocated to the control condition will get usual care (slightly enhanced) alone. The WHO recommends eight antenatal visits for positive pregnancy experience (43) which we will be the target number of visits for study participants in the control group (depending on their gestational week). These visits will involve evaluating health status, discussing any concerns, and performing routine exams consistent with stage of pregnancy. Usual care will also be enhanced by medical staff at the hospital receiving additional training in mental health treatment to counsel participants. Transportation will also be provided or facilitated for participants to assist with attending appointments and the study will pay for any ultrasounds needed.

3. Will you use a placebo or non-treatment group, and is that justifiable?

The control arm will receive a slightly enhanced version of usual care, which we consider is justifiable.

4. Explain when you may remove a participant from the study.

Missed sessions or early withdrawal (i.e., withdrawal before all sessions are completed) from the HMHB intervention or from the schedule of visits for the control group, will not result in investigator/research team-initiated withdrawal from the study; in such cases of missed visits, remaining study procedures can and should be completed as indicated by the study protocol. If a clinically significant finding is identified (including but not limited to changes from baseline) after enrollment, the HBHM trainer, assessor or hospital staff will refer the case to Co-I Dr. Najia Atif (a psychologist and the main intervention supervisor) and Co-I Dr. Abid Malik (a psychiatrist and the main field supervisor) to determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

Participants are free to withdraw from the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Death of participant.
- Women who develop suicidal ideation who are unable to participate because of their care
- Participant moves from the study area.
- Acute, chronic, or long-term physical or psychiatric illness in the participant leading to inpatient hospitalization during the study
- Any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression that requires discontinuation of the intervention

The reason for participant termination or withdrawal from the study will be recorded. Women with a miscarriage, stillbirth or neonatal death before the 6 week postpartum visit will still be included in the study for the 6 week postpartum mental health outcomes, although they may not be able to provide data for other child-related outcomes.

A participant will be considered lost to follow-up if he or she fails to return to the endpoint assessment (i.e., 6 weeks postpartum) and/or is unable to be contacted by the study site staff.

The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- The study team will attempt to contact the participant, reschedule the missed visit in a subsequent week, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, three telephone calls and a call to any designated family friends for whom the participant has provided a contact phone number in case of loss to follow-up, and if necessary, a certified letter may be sent to the participant's last known mailing address). These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study as lost to follow-up.

5. What happens to participants on study intervention when the study ends?

Participants will continue to receive their usual care at HFH (and/or elsewhere)

6. Describe the process for referring participants to care outside the study, if needed.

Prior to initiation of the study, all medical staff based at the Department of Obstetrics of HFH will be trained/oriented in WHO's mhGAP guidelines to address take part in the process of making referrals from non-specialist providers or interviewers. Such referrals will be made to the Institute of Psychiatry (IoP) in Rawalpindi, the district tertiary care hospital, or the teaching hospital. These centers are staffed by experienced and qualified psychiatrists and other mental health professionals who routinely provide a range of services. The IoP is also the WHO Collaborating Centre for Mental Health Research and Training in Pakistan. They also have an established social services for persons affected by domestic violence.

Any woman showing signs of severe depression or suicidality at any point during the study will be noted by the HMHB trainer or assessment team members or hospital staff (antenatal staff) and reported to Dr. Najia Atif a psychologist Dr. Abid Malik, a psychiatrist for further evaluation. Based on their clinical judgement referred psychiatric and/or psychological care as is necessary. As mentioned above HMHB therapists, the assessment team and hospital staff in the Obstetrics Department will be trained in the WHO's mhGAP guidelines. For a woman without life-threatening conditions but with high symptom levels of anxiety or depression, her obstetrician will be alerted to undertake further assessment and to make appropriate referrals. Women who report IPV will be referred to the IoP for social services. Because domestic

violence against women is highly prevalent in Pakistan, we are in the process of reviewing additional potential interventions strategies to be incorporated in the HMHB intervention program. Women needing general medical care will be referred within the hospital facilities.

VI. Data Security and Confidentiality Protections:

1. Personally Identifiable Information (PII):

Please identify the Personally Identifiable Information (PII) that you may be collecting and using at any of the following stages of your study: ***Recruitment***, ***Consent,*** *and* ***Study Implementation***.

Name, signature, initials, or other identifiable code	☒
Geographic identifier: address, GPS location, etc.	☒
Dates: birth, death, clinical service, discharge, etc.	☒
Contact information: phone numbers, email address, etc.	☒
ID: Social Security Number, driver's license number, etc.	☐
Health record identifiers: medical record, insurance plan number, etc.	☒
Account numbers	☐
Device identifiers: e.g., implants	☐
Internet identifiers: IP address, social media accounts	☐
Biometric identifiers, including finger and voice prints	☐
Audio recordings	☐
Video or full face photographic images	☐
Genomic/genetic data	☐
Any other unique identifying number, characteristic, or code (note: this does not mean the unique code assigned by the investigator to code the data)	☐
Other: Click here to enter text.	☐

2. Recruitment:

Will you collect identifiers for the purpose of contacting potential participants? Yes ☒ No ☐

If **yes**, will you retain the identifiers after the recruitment contact has been made? Yes ☒ No ☐

3. Data Collection:

Collection of data for a research study can take on many forms. It can be as simple as gathering the data with pen and paper or developing an on-line adaptive survey that changes based on the participant's answers. Regardless of the method, PII for the purposes of identifying the participants will most likely be collected. Once collected, the raw data should go through a de-identification process to further protect PII.

In what form will you collect and store PII? When you respond, think of PII collected for recruitment, consent, and other study purposes.

1. **Hard Copy/Paper:** Yes ☒ No ☐

If yes, please answer the following:

A. How will the data be kept secure during transfer from study collection site to storage site?

Any data in the form of paper or hard copies (i.e. consent forms, log of women screened) will be kept in a locked bag to be carried by one of our research staff members to the central HDRF office where the data manager will also have an identical set of keys to open the bag. These data should be delivered by means of same-day dispatch. Paper documents with personal information including consent forms will be kept in a locked filing cabinet. The key will be kept with the data manager. All personal information will be confidential and will not be shared or discussed with individuals outside the team without participant consent (e.g. in the case of a clinical referral). Encrypted study participant research data, which is for purposes of statistical analysis and scientific reporting, will be collected on tablets. These tablets will be connected to a central server and transmitted to and stored at the HDRF data coordinating center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry (e.g. the tablets) and study management systems used by the clinical site, by the HDRF data Coordinating Center and research staff will be secured and password protected. This password will be updated on a monthly basis. After each wave of data collection data will also be sent to JHSPH and stored on JHBox. At the end of the study, all study databases will be de-identified and archived at the NIMH data repository.

Biological data will be generated by Dr. Osborne and will be stored on a secure server in the Department of Psychiatry.

B. Will the data be secured in a locked cabinet or room? Yes ☒ No ☐

C. If study IDs/Codes are used, will they be stored separately from the study data? Yes ☒ No ☐

D. Will the hard copy/paper be destroyed after data abstraction and cleaning are complete?
Yes ☒ No ☐
If No, when do you plan to destroy the hard copies?

2. **Electronic:** Yes ☒ No ☐

If yes, please answer the following:

- Will the data be collected/stored on a portable device (laptop, mobile phone, tablet, PDA) protected by encryption? Yes ☒ No ☐

- Will study participants use personally owned devices or study-provided devices?
Personally owned ☐ Study provided ☒

- Is the application/website used for data collection being developed in-house (Hopkins) or by a 3rd party vendor?

In-house ☐ 3rd party ☒

If 3rd party, provide the name of vendor and URL:
Identify Mobile Ecosystem (check all that apply) Apple ☐ Google ☒ Website ☐

- Will the data be stored on a secure server (@JHSPH/on-site)? Yes ☒ No ☒

- Will the data be stored in the Cloud/Web? Yes ☒ No ☐
- Will it be encrypted? Yes ☒ No ☐
- Will you be backing up your data? Yes ☒ No ☐

3. **Audio Recording:** Yes ☐ No ☒

If yes, please answer the following:

1. Will you store the audio recording securely in a locked cabinet/room until transcription is complete?
   Yes ☐ No ☐
2. Will you use a transcription service?
   Yes ☐ No ☐
   If yes, if the PII comes from JHH/JHHS, you must use an approved vendor; otherwise, be aware of the data security protections that the transcription service provides.
3. Will the audio recording be destroyed after transcription? Yes ☐ No ☐

   If no, why not?

- **Photograph/Video:** Yes ☐ No ☒

If yes, please answer the following:

- Will the photographs/videos be stored securely in a locked cabinet or room? Yes ☐ No ☐
- Will the photograph/video be destroyed? Yes ☐ No ☐

  If yes, when?

4. PII De-Identification of Data Used for this Study:

- When will you destroy the PII and/or the code linking the PII with the study ID?

While the data will be deidentified for the purposes of analysis, the data code linking the PII and study ID will be destroyed after analysis of these data is complete.

- What is the method you will use to de-identify the data?

At the end of the data collection period and after all data has been cleaned, analytic datasets will be stripped of names of participants. Datasets will retain the unique study number for each participant.

- Is your research data governed by HIPAA (U.S. clinical data remaining within the covered entity)?
  Yes ☐ No ☒
  - If yes, who is doing the de-identification?
  - If yes, what level of de-identification will you achieve (Limited data set? De-identified?)

5. Data Storage and Analysis:

One of the keys to protecting PII is the proper use of tools to share and conduct your analysis. JH and JHSPH offers several options for you to consider. Please select the system that you plan to use to protect your study data by clicking the box. Consult JHSPH IT for assistance if needed.

☐ **JH Virtual Desktop**: The Hopkins Institute for Clinical and Translational Research (ICTR) provides a virtual Windows desktop (SAFE Desktop). It includes productivity software such as Microsoft Word and Excel, as well as statistical software, including SAS, Stata, R, R Studio, and Python. 100 GB of storage space is provided.

☐ **JHSPH SharePoint and File Shares**: These systems provide a managed and secure platform for your research project. They also provide a built-in encrypted backup solution.

☐ **JHSPH RedCAP**: These are departmentally managed applications. RedCAP is an application designed for collaborative research projects.

☐ **JHSPH HPCC:** High Performance Computing Cluster (HPCC: https://jhpce.jhu.edu/) can provide the high capacity computing required for very large data sets.

☒ **JHBox**: Johns Hopkins Box (JHBox) is a secure cloud-based file sharing service which enables people to collaborate and share information and may be accessed through any device: desktop, laptop, phone, or tablet with appropriate permissions. JHSPH IT recommends that investigators not use JHBox as a primary storage location, but use it instead for initial data collection, sharing results, and other collaborative information with the research team.

☐ **Independent Departmental Servers and Systems**: These servers are typically managed by departmental or research team IT staff. Because these servers are not centrally managed by JHSPH IT, all documentation regarding data security protections will need to be provided by the owner/administrator of the server. This responsibility may fall to the data owners (PI).

☒ **Other**: Please provide details regarding any other systems being utilized. Examples may include servers and applications located at another university participating in your study or a 3rd party web-based application.

Any data in the form of paper or hard copies (i.e. consent forms, log of women screened) will be kept in a locked bag to be carried by one of our research staff members to the central HDRF office where the data manager will also have an identical set of keys to open the bag. These data should be delivered by means of same-day dispatch. Paper documents with personal information including consent forms will be kept in a locked filing cabinet. The key will be kept with the data manager. All personal information will be confidential and will not be shared or discussed with individuals outside the team without participant consent (e.g. in the case of a clinical referral). Encrypted study participant research data, which is for purposes of statistical analysis and scientific reporting, will be collected on tablets. These tablets will be connected to a central server and transmitted to and stored at the HDRF data coordinating center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry (e.g. the tablets) and study management systems used by the clinical site, by the HDRF data Coordinating Center and research staff will be secured and password protected. This password will be updated on a monthly basis. After each wave of data collection data will also be sent to JHSPH and stored on JHBox. At the end of the study, all study databases will be de-identified and archived at the NIMH data repository.

During data collection at the hospital, all the data collected on tablets will be submitted on the server via internet at the end of each working day. No data will remain on tablets at the end of the day. The data will be sent to the HDRF server on daily basis once the interview is over. The Assessment Team members will confirm with the HDRF data manager that he has received the submitted forms. Data will not be deleted from tablets without the consent of the data manager. Open Data Kit (ODK) forms are autosaved so that there is no chance of losing the data. The assessment team and the data manager will remain in communication to ensure proper management of data. The data manager will check the online submission of data before closing of each day and will verify the submission of data on the web server on daily basis. The data manager must make daily backups of the trial data and will keep those backups both at Holy Family Hospital and at the HDRF office. Only the data manager will have access to the ODK web server. The data manager will share a weekly report with the site PI and project manager including an enrollment table that will have the screening details of the trial participants and their numbers per trial arm. The data manager and trial manager will make a weekly report (including SAE, refusal cases, missing data etc.) to be shared at the end of each week with PI. The informed consent forms will be stored in a separate HMHB locked cupboard and their log must be maintained by the assessment team lead, it will be checked on daily basis for the correct date, signature or thumb prints (whichever is applicable). At the end of each day, a data cleaning process will take place before finalization and sending the forms.

6. **Other Data Security Measures:**

In addition to the details regarding data collection, please review the following questions. This additional information will be utilized to assist in the development of a comprehensive Data Security plan. This would include the systems used to analyze the data, data security contacts and additional requirements.

1. During the analysis phase, do you plan to use computer systems that are not managed by JHSPH or JH? Yes ☒ No ☐

   If yes, please explain: The team in Pakistan will have the data on their server at HDRF as it is collected. (See #5 above on page 21-22)

2. Do you have a designated person on your research team other than the PI who is the technical contact for a Data Security plan? Yes ☒ No ☐

   If yes, please provide a contact name: Ahmed Zaidi.

10. Does your sponsor have other specific data security requirements for the study data? Yes ☐ No ☒

    If possible, please explain:

3. Please add any other information that you believe is relevant to data security.

4. Certificate of Confidentiality:

All NIH studies include Certificate of Confidentiality protections with the grant; the consent form must include the C of C language provided in our template. Other funders may obtain C of C protections through NIH. (https://humansubjects.nih.gov/coc/index)

Does the study have Certificate of Confidentiality protections?

Yes ☒ No ☐

5. **JHM Clinical Records:**

Will you use clinical data of 500 records or more from Johns Hopkins Hospital and its affiliates?
Yes ☐ No ☒

If yes, please complete the JHM Data Security Checklist available on the JHSPH IRB website: www.jhsph.edu/irb and upload a copy of the checklist to the "Miscellaneous" section.

VII. Risks of the Study:

- Describe the risks, discomforts, and inconveniences associated with the study and its procedures, including physical, psychological, emotional, social, legal, or economic risks, and the risk of a breach of confidentiality. These risks should be described in the consent documents.

The proposed HMHB intervention is based on tried and tested principles of CBT, which are safe and effective and considered one of the first lines of treatment for anxiety (77)

We do not foresee any potential long-term risks associated with the intervention. Potential immediate risks and discomforts anticipated with the research procedures are given below:

- Pregnant women may find it difficult to talk about
  - stressful experiences in their lives while answering structured questionnaires containing scales (e.g., about CMDs, healthcare utilization, etc.) resulting in distress.
  - experiences of intimate partner violence (IPV) while answering structured questionnaires.
- HMHB non-specialist providers may find working with anxious or depressed individuals distressing.
- Non-specialist providers may divulge information about anxious or depressed women to others, a breach of confidentiality.
- A large number of survey measures could cause respondent burden.
- Blood draw: Risks are minimal but include temporary discomfort, bleeding or bruising and rarely infection and light-headedness/fainting. If light-headedness/fainting occurs the subject will be monitored by a member of the research team and will not be released until the event has resolved.

- Describe the anticipated frequency and severity of the harms associated with the risks identified above; for example, if you are performing "x" test/assessment, or dispensing "y" drug, how often do you expect an "anticipated" adverse reaction to occur in a study participant, and how severe do you expect that reaction to be?

We expect the severity of the discomfort of participation in intervention sessions and questionnaire completion to be no greater than what women experience normally while talking about their feelings in daily life. We also believe that the possibility of breach of confidentiality and stigmatization is very low. All the interviewers and non-specialists piloting the intervention content will be trained on maintaining confidentiality. All of the research staff will be trained to use non-stigmatizing terms/language. Similarly, the intervention content will use non-stigmatizing terms/ language. Adverse events related to the blood draw are expected to be extremely infrequent.

- Describe steps to be taken to minimize risks. Include a description of your efforts to arrange for care or referral for participants who may need it.

Plan to minimize risk (a): Study staff members who administer questionnaires to participating women will be trained to be sensitive and to identify any psychological symptoms/distress that participating women may experience while answering the questionnaires. Although we will be using non-specialized providers as HMHB Trainers, staff trained in counseling will be available, who can be called upon if participants are mildly distressed. For more severe distress we will follow hospital protocols for referral/services.

Also, prior to the initiation of the study, all medical staff based at the Department of Obstetrics will be trained/oriented in the WHO Mental Health Gap Action Program (mhGAP) treatment guidelines to address any

referrals from the research team. Apart from the training of medical staff of hospital, referrals will be made to the Institute of Psychiatry (IoP), Rawalpindi, the district tertiary care hospital.

Additionally, to reduce the burden on women participating in the study we will provide the option of taking breaks between questionnaire sections and/or have the option of having the questionnaire administered in two sittings. Participants will be instructed that they may decline to answer or discontinue participation from the study at any time.

A. Participants may find it difficult to talk about experiences of intimate partner violence (IPV) in their lives while answering structured questionnaires.

Plan to minimize risk (B): We recognize IPV is an issue that is associated with both anxiety and depression. It has high prevalence rates in urban Pakistan (47). All women will be assessed on a IPV screener at the baseline and 3rd trimester visits as well as the 2013 DHS IPV instrument at the six-week postpartum visit. This will allow us to identify any women needing referrals because of IPV. All women participating in the study regardless of study arm will receive information about where they can seek care for IPV (i.e. the Institute of Psychiatry.) This program, like our prior Thinking Healthy Program (THP) that used CBT to reduce depression, includes several components – related to family engagement, education, problem solving, facilitating women to tap into their support networks– that will help address potential IPV. We have also identified potential interventions based on the WHO's Problem Management+ (PM+) (48, 49) for IPV, which are being reviewed in detail before the start of the trial. Women who report IPV will be referred to the Institute of Psychiatry, Rawalpindi Medical College, where they can receive social services and support for IPV.

B. **There may be some women experiencing extreme distress.**

This issue will be addressed in the following way:

Step 1: We will exclude depressed cases at the screening stage and refer them to their physician at the hospital (who will have been given mhGAP training). If a woman is suicidal then she will be referred to psychiatric and/or psychological care the hospital. For non-life threatening less extreme distress, but high symptom levels of anxiety or depression, the participant's obstetrician or primary care provider will be alerted to undertake further assessment and to make appropriate referrals.

Step 2: For any women who may develop depression during the trial (who were not depressed at baseline/enrollment), we will follow the same procedure for referrals (above). Evaluation of whether depression is developed will be based on identification from the HMHB trainer, a member of the assessment team, or hospital staff (who will have all received MhGAP training in mental health). If they find someone they suspect who is developing depression, they will contact Co-I Dr. Najia Atif (a psychologist) and Co-I Dr. Abid Malik (a psychiatrist) to further investigate and determine when referrals are necessary. The HMHB trainers will be regularly supervised by Dr. Atif (the master trainer) and the assessors will be regularly supervised by Dr. Malik (the site psychiatrist).

C. HMHB non-specialist providers may also find working with anxious or depressed individuals distressing.

Plan to minimize risk (D): HMHB Trainers (the intervention team) will receive weekly group supervision sessions by the mental health specialist (Co-I Dr. Najia Atif) trained in the Cognitive Behavioural Therapy and the Person-Centered Counselling and an obstetrician (Co-I Dr. Shamsa Zafar). NA has experience supervising the non-specialist providers for the South Asian Hub for Advocacy, Research, and Education (SHARE) Program. As a routine procedure, issues related stress will be explored and addressed during supervision sessions. In the case of the non-specialist providers experiencing unusually challenging situations that cause mental distress, we will instruct non-specialist providers to contact the supervisor between supervision sessions. If the supervisor recognizes any ongoing signs of anxiety or depression in the non-specialist providers or if it has been reported to her, it will be explored in-depth by arranging individual supervision

for the non-specialist provider. If it has been determined that the non-specialist provider is experiencing severe distress, adversely impacting her psychological wellbeing and/or hindering to her role in delivering the intervention, then she will be relieved from her duties and referral will be made following the established protocol for referral/services (that has been outlined for participating women).

D. There is a risk of the non-specialist providers divulging information about anxious or depressed women to others – thus breach of confidentiality and risk of stigmatization from CMDs may be possible.

Plan to minimize risk (E): Non-specialist providers and interviewers collecting data for the study will be trained and supervised on how to intervene with women with CMDs and their families, how to monitor worsening of symptoms using mood charts and when and where to refer participating women. Training and supervision will also cover the issue of maintaining confidentiality of the intervention participants.

Regular supervision meetings with the study's non-specialist providers will also ensure all of these risks are minimized. These group supervision meetings will additionally allow the non-specialist providers the opportunity to discuss and address their own distress from working with anxious or depressed pregnant women.

E. Large number of survey measures could lead to respondent burden.

Plan to minimize risk (F): We will be mindful of the burden on participants and will streamline the data collection process by training our research staff both to 1) make data collection efficient, and 2) be sensitive to participant fatigue and signs of distress.

In order to prevent as much respondent burden as possible, we will provide participants the option of taking breaks between questionnaire sections and/or having the option to complete the questionnaires in two sittings. Finally, research staff trained in counselling techniques will be available who can be called upon if participants are mildly distressed. For more severe distress we will follow the protocol for referral/services outlined in our human subjects section.

Also, to protect against risks and monitor the trial and activities described, a Trial Steering Committee (TSC) consisting of Drs. Surkan, Zafar, Atif, Malik, Rahman, Mullany, Chaudhri, Hamdani, the data manager (TBD) and representatives of the NIMH will oversee this study and take necessary steps to further mitigate any potential risks. The TSC will meet before the trial commences to approve the final protocol and on a weekly basis to monitor trial conduct and progress. Meeting minutes will be kept to document ongoing issues, to keep the study on track, and to ensure that steps are taken to address any issues needing attention and that they dealt with appropriately. The TSC will also submit progress reports with updates to the local IRB at the Human Development Research Foundation (HDRF) as well as the Data Safety and Monitoring Board (DSMB).

F. Blood Draws

Plan to minimize Risk F: The blood will be drawn by a trained professional (physician, nurse, phlebotomist, or trained study team member). In all cases, aseptic technique will be practiced while obtaining the venous blood samples. If lightheadedness or syncope occurs the subject will be monitored by a member of the research team and not released until resolved. If any unforeseen complication occurs, the patient will be examined by a physician and an appropriate course of action as determined individually and as medically warranted. All personnel will undergo training for safe handling and storage of bodily fluids.

COVID-19 Exposure Contingency Plans

Research team members who are found to be COVID-19 positive or experience unprotected exposure to COVID-19 will be referred to care, sent home or to the appropriate facility for required treatment, and instructed to self-isolate. These team members will not have subsequent interaction with study participants before resolution of their infection, with al research study visits or other in-person activities being transferred to other staff or rescheduled to avoid exposure of participant or other staff. The staff members' equipment and workplace will be sanitized.

COVID-19 positive or exposed research study participants will be referred for appropriate testing and/or treatment and will be interviewed by phone or in person to determine possible contacts among other study participants or study staff and facilitate contact tracing. These participants will not engage in any in-person study activities until resolution of their infection. Study staff who interacted with these participants without appropriate PPE will not carry out further in-person duties until they are tested and/or complete 14 days of isolation.

- Describe the research burden for participants, including time, inconvenience, out of pocket costs, etc.

Participants may feel tired or upset by talking about stressors or concerns that make them anxious. We will allow them to take breaks if they feel the interview is long or that they would like to take a break. We will also offer them counseling, if they indicate the need for it or if we consider that they could benefit from it. We will reimburse women for transportation costs to interviews and intervention group sessions.

- Describe how participant privacy will be protected during data collection if sensitive questions are included in interviews.

All interviews and sessions will be conducted, to the extent possible, in privacy. The assessment team and non-specialist providers will be trained to explain to family members (accompanying the participant) why it is important for the interview/session to be carried out privately, unless the participant requests for family member/s to be present.

VIII. Direct Personal and Social Benefits:

- Describe any potential direct benefits the study offers to participants ("payment" for participation is not a direct personal benefit).

Individual benefits: Participation in this study may confer both physical, psychological, and other benefits. First, CBT methods that are indicated for anxiety(50) will be used to address major stressors during pregnancy. These methods have the potential to directly help women and reduce symptoms of anxiety, as well as have beneficial effects on depression (which is highly correlated with anxiety and for which symptoms of anxiety are a risk factor). Women in the intervention and control groups who are identified as having life-threatening mental health conditions (i.e., severe depression or active suicidal ideation) will be referred immediately for psychiatric and/or psychological care. Ultrasound re-imbursement will also be a benefit of the study.

- Describe potential societal benefits likely to derive from the research, including value of knowledge learned.

Societal Benefits: The research has the potential to make a major contribution toward addressing prenatal anxiety, which could have downstream benefits to prevent both later anxiety and depression as well as adverse outcomes for children. It will advance our knowledge regarding whether such an intervention can achieve benefits for mothers and their children in these domains. In addition, the analysis of mediators will provide the opportunity to learn about potential mechanisms that could be targeted to enhance the intervention upon scale-up. Evaluation of effect modifiers is important for this research as it allows us to learn in which subgroups of women

the intervention may be more or less effective. The economic evaluation will also inform how available funds can be used most efficiently, providing useful policy-relevant information needed for the potential scale-up of such a program. If successful, the HMHB intervention could provide evidence to inform more effective public health interventions and public policies to promote lifelong maternal mental health and resilience across generations and provide information to inform resource budgeting for such programs.

IX. Payment:

1. Describe the form, amount, and schedule of payment to participants. Reimbursement for travel or other expenses is not "payment," and if the study will reimburse, explain.

Pregnant women participants may receive approximately equivalent to $4.00 US dollars as a thank you for their time and to facilitate transportation. They will also receive reimbursement for ultrasound scans during the course of their pregnancies (normally charged by the hospital, which cost ~$1.00), as indicated by the obstetrician/gynecologist taking care of the participant. We will also give each mother a present in the form of children's clothes as a token of our appreciation at the conclusion of the study (~$4.00 USD). For women who have lost a fetus or baby we will give them the equivalent in household items. Women who participate in the biological substudy will also receive a baby gift worth approximately $10 US.

2. Include the possible total remuneration and any consequences for not completing all phases of the research.

X. Study Management:

A. Oversight Plan:

1. Describe how the study will be managed.

The Trial Steering Committee (TSC) is comprised of key personnel from research team, a NIMH Program Official and a DSMB liaison. The TSC is chaired by the study PI and Site Co-PIs. The PI and Site Co-PIs will be primarily responsible for monitoring the trial. All the named investigators have previously conducted clinical trials of this type. The PI will be in regular contact with the local investigators and staff via trial management structures, as well as additional in-person contact or via email, when required. The trial steering committee will meet between once a week (during enrollment) to once a fortnight (following enrollment until the completion of the trial). Its role is to monitor all aspects of the conduct and progress of the trial and ensure that the protocol is adhered to.

2. What are the qualifications of study personnel managing the project?

Membership of TSC

NAME	Position and Affiliation
Pamela Surkan	(PS; PI), Johns Hopkins Bloomberg School of Public Health, USA
Atif Rahman	(AR; Co-I), University of Liverpool, UK
Rizwana Chaudhri	(RC; Co-I), Holy Family Hospital, Rawalpindi, Pakistan
Abid Malik	(UH; Co-I, co-site PI), Human Development Research Foundation, Pakistan
Shamsa Zafar	(SZ; Co-I, co-site PI), Health Services Academy, Pakistan
Najia Atif	(NA; Co-I), Human Development Research Foundation, Pakistan

Luke Mullany	(LM; Co-I and trial statistician), John Hopkins Bloomberg School of Public Health, USA
Sharon L. Smith	(SLS; Program Coordinator), NIMH, USA
Makeda Williams	(MH; Program Officer), Chief, Global Mental Health Effectiveness Research Program, NIMH, USA
TBD	(Data Manager), Human Development Research Foundation

Drs. Rahman, Zafar, Malik, Sikander and Atif have extensive experience carrying out research and trials in Pakistan and have developed specific, detailed procedures to use while collecting, handling and storing data from clinical trials in South Asia.

I will highlight Dr. Malik's experience (the local PI):

Dr. Malik is a consultant psychiatrist and honorary senior lecturer at University of Liverpool who has trained in Pakistan and United Kingdom. He has over 23 years of experience of working in clinical and research settings. He had been the site PI of Thinking Healthy Program and followed a cohort of antenatal depressed women for a year in rural Pakistan to complete his PhD. He has expertise of managing data collection, training of teams and providing input into research protocols. Dr. Malik extensive clinical and research experience would enable the assessment team to reach the targets in time.

3. How will personnel involved with the data collection and analysis be trained in human subjects research protections? (Use the JHSPH Ethics Field Training Guide available on the JHSPH IRB website: www.jhsph.edu/irb.)

The Pakistani team from Liverpool and Human Development Research Foundation -- HDRF (Rahman, Zafar, Malik, Chaudhri and Atif) have previously completed the Human Participant Protections Education for Research Teams online courses, sponsored by NIH. The team from Johns Hopkins University (Surkan and Mullany) has completed the CITI human subjects training through the Bloomberg School of Public Health.

4. If the PI will not personally be on-site throughout the data collection process, provide details about PI site visits, the supervision over consent and data collection, and the communication plan between the PI and study team.

The PI will have weekly calls with the team, and local supervision of consent and data collection will be monitored by Drs. Malik and Zafar (as described above in #1). The PI will also make at minimum yearly site visits. The leadership team will meet in Baltimore and Liverpool once a year for face-to-face team meeting (including not only Drs. Surkan, Rahman, Zafar, Malik and Atif but also including Dr. Mullany). Drs. Stuart and Frick will participate in the Baltimore based face-to-face meetings.

B. **Recordkeeping:**
Describe how you plan to ensure that the study team follows the protocol and properly records and stores study data collection forms, IRB regulatory correspondence, and other study documentation. For assistance, contact housecall@jhu.edu.

Drs. Malik and Zafar, as the local–PIs, will be monitoring this regularly. During our weekly calls the PI will inquire and monitor any issues about how these records are being stored and data collected. Furthermore, the PI will check on this during site visits. Other study documentation can be sent to the PI at Hopkins for review. An NIMH appointed Data Safety and Monitoring Board will also be included in our calls and will provide additional advice and guidance as any issues come up. During the formative phase (IRB #7678) representatives from the IRB joined regularly in our monthly research management meetings. They have indicated that they will also attend our meetings during the trial phase.

C. **Safety Monitoring:**

1. Describe how participant safety will be monitored as the study progresses, by whom, and how often. Will there be a medical monitor on site? If yes, who will serve in that role?

Throughout the study, the TSC will provide updates on regulatory matters, recruitment, safety issues and works closely with Data Safety and Monitoring Board (DSMB). The TSC will oversee this study and take necessary steps to further mitigate any potential risks. The DSMB will inform the TSC of any signals or concerns regarding the protection of participant safety. The DSMB has decision making authority, and decisions made by the DSMB will not require ratification by the investigators. The TSC will also submit progress reports/updates to the local IRB at HDRF as well as the DSMB.

2. If a Data Safety Monitoring Board (DSMB), or equivalent will be established, describe the following:

   a. The DSMB membership, affiliation and expertise.

      This has been determined by NIMH

   b. The charge or charter to the DSMB.

      TBA

   c. Plans for providing DSMB reports to the IRB.

      TBA

6. Describe plans for interim analysis and stopping rules, if any.

   We have no plans for interim analyses for the effects of the trial or stopping plans.

D. **Reporting Unanticipated Problems/Adverse Events (AEs) to the IRB (*all studies must complete this section*)**:
Describe your plan for reporting to the IRB and (if applicable) to the sponsor. Include your plan for government-mandated reporting of abuse or illegal activity.

- AEs detected by the assessment team will be collected systematically on smart phones/tablets (electronic data collection) during all outcome assessments. These will be uploaded daily to the database and the data manager will complete a daily report (detailing the participant's Trial ID, type of AE and date of the event) and forward this to the Dr. Abid Malik (Co-I).
- AEs detected by the non-specialist providers will be first reported to Dr. Abid Malik (one of the site PIs) who will complete the AE report on smart phones/tablets. These will be uploaded to the database and the data manager will complete the report (detailing the Trial ID, type and date of the event) and forward it to the study coordinator.
- The data manager will forward the AEs to the nominated independent psychiatrist, Dr. Fakhra, MBBS (Department of Obstetrics and Gynecology at HFH) who is not associated with the research study or to an independent physician. Dr. Fakhra will do a home visit or have a telephone call with the respective participant or family member in the case of death to inquire about the details of the event and to suggest mitigation strategies (as outlined above). This assessment will be documented in a detailed narrative report regarding the nature of the AE, its relationship to the intervention, actions taken since then and actions recommended.
- The data manager will mask the participant's identity (by eliminating any identifiable information) and send these detailed narrative reports to Dr. Abid Malik (one of the site PIs) who will in turn forward this information to the PI.
- The site PIs will forward this report to the local IRB as well as document it in periodic updates for JHU.

NOTE: The IRB does not require PROMPT reporting of all AEs, only those that are **unanticipated, pose risk of harm to participants or others, and are related to the study**. Anticipated AEs may be reported with the Progress Report.

E. **Other IRBs/Ethics Review Boards:**

If other IRBs will review the research, provide the name and contact information for each IRB/ethics review board and its Federal Wide Assurance, if it has one (available on OHRP's website at http://www.hhs.gov/ohrp/assurances).

Federal Wide Assurance No: FWA 00010167, Human Development Research Foundation (HDRF), Islamabad, Pakistan

F. **Collaborations with non-JHSPH Institutions:**

For studies that involve collaboration with non-JHSPH institutions, complete the chart below by describing the collaboration and the roles and responsibilities of each partner, including the JHSPH investigator. This information helps us determine what IRB oversight is required for each party. Complete the chart for all multi-collaborator studies.

Insert Name of Institutions in Partner column(s); add additional columns if necessary.

	JHSPH	Partner 1 Human Development Research Foundation	Partner 2 University of Liverpool
Primary Grant Recipient	X		
Collaborator		X	
Collaborator			X

For the following, indicate "P" for "Primary", "S" for "Secondary" (as appropriate to role and level of responsibility.) Add additional items if useful.

1.	Human subjects research ethics training for data collectors	S	P	
2.	Day to day management and supervision of data collection		P	
3.	Reporting unanticipated problems to the JHSPH IRB/Sponsor	P		
4.	Hiring/supervising people obtaining informed consent and/or collecting data		P	
5.	Execution of plan for data security/protection of participant data confidentiality, as described in the Data Security and Confidentiality Protections section above	S	P	
6.	Biospecimen processing, storage, management, access, and/or making decisions about future use	--	--	--

COMPLETE THE FOLLOWING SECTIONS WHEN RELEVANT TO YOUR STUDY:

XI. Secondary Data Analysis of Existing Data:

A. Study Design:

1. Describe your study design and methods. The study design must relate to your stated aims/objectives.

2. Provide an estimated sample size and an explanation for that number.

1. Provide a brief data analysis plan and a description of variables to be derived.

B. Participants:

1. Describe the subjects who provided the original data and the population from which they were drawn.

2. If you are receiving, accessing, or using data from a U.S. health care provider, the need for HIPAA review is likely. If you plan to bring identifiable health information from a foreign country to a U.S. covered entity (e.g., lab at the Hopkins SOM), HIPAA may be triggered. If either of these conditions is met, check "yes" to the HIPAA question in the PHIRST application.

1. If you plan to analyze human specimens or genetic/genomic data, provide details about the source of those specimens and whether they were collected using an informed consent document. If yes, explain whether your proposed use is "consistent with" the scope of the original consent, if it potentially introduces new analyses beyond the scope of the original consent, and/or if it introduces new sensitive topics (HIV/STDs, mental health, addiction) or cultural/community issues that may be controversial.

XII. Oversight Plan for Student-Initiated Studies:

1. For student-initiated studies, explain how the PI will monitor the student's adherence to the IRB-approved research plan, such as communication frequency and form, training, reporting requirements, and anticipated time frame for the research. Describe who will have direct oversight of the student for international studies if the PI will not personally be located at the study site, and their qualifications.

2. What is the data custody plan for student-initiated research? *(Note: Students may not take identifiable information with them when they leave the institution.)*

XIII. Creation of a Biospecimen Repository:

Explain the source of the biospecimens, if not described above, what kinds of specimens will be retained over time. Clarify whether the specimens will be obtained specifically for repository purposes, or will be obtained as part of the core study and then retained in a repository.

a. Describe where the biospecimens will be stored and who will be responsible for them.

b. Describe how long the biospecimens will be stored, and what will happen at the end of that period.

c. Explain whether the biospecimens will be shared with other investigators, inside and outside of JHU, how the decision to share will be made, and by whom. Include your plans, if any, for commercial use. Also explain how downstream use of the specimen will be managed, and what will happen to left-over specimens.

d. Describe whether future research using the biospecimens will include specimen derivation and processing (cell lines, DNA/RNA, etc.), genomic analyses, or any other work which could increase risk to participants. Explain what additional protections will be provided to participants.

e. If future research could yield unanticipated incidental findings (e.g., an unexpected finding with potential health importance that is not one of the aims of the study) for a participant, do you intend to disclose those findings to the study participant? Please explain your position.

f. Explain whether the specimens will be identifiable, and if so, how they will be coded, who will have access to the code, and whether the biospecimens will be shared in linked (identifiable) form.

g. Explain whether the repository will have Certificate of Confidentiality protections.

h. Explain whether a participant will be able to withdraw consent to use a biospecimen, and how the repository will handle a consent withdrawal request.

i. Describe data and/or specimen use agreements that will be required of users. Provide a copy of any usage agreement that you plan to execute with investigators who obtain biospecimens from you.

XIV. Data Coordinating Center:

Complete if JHSPH serves as the Data Coordinating Center.

1. How will the study procedures be developed?

2. How will the study documents that require IRB approval at each local site be developed? Will there be some sort of steering or equivalent committee that will provide central review and approval of study documents, or will template consent forms, recruitment materials, data collection forms, etc. be developed by and provided to the local sites by the coordinating center without external review?

3. Will each local clinical site have its own IRB with an FWA? State whether the coordinating center will collect IRB approvals and renewals from the clinical centers; if not, explain why.

4. How will the coordinating center provide each local site with the most recent version of the protocol and other study documents? What will be the process for requesting that these updates be approved by local clinical center IRBs?

5. What is the plan for collecting data, managing the data, and protecting the data at the coordinating center?

6. What is the process for reporting and evaluating protocol events and deviations from the local sites? Who has overall responsibility for overseeing subject safety: the investigators at the recruitment site, the Coordinating Center, the Steering Committee, or a Data and Safety Monitoring Board (DSMB)? Is there a DSMB that will evaluate these reports and provide summaries of safety information to all the reviewing IRBs, including the coordinating center IRB? Please note that if there is a DSMB for the overall study, then the coordinating center PI does not have to report to the coordinating center IRB each individual adverse event/problem event that is submitted by the local site PIs.

7. Some FDA regulated studies have different AE reporting criteria than that required by the IRB (IRB Policy No. 103.06). How will you reconcile the different requirements, and who is responsible for this reconciliation?

8. Who is responsible for compliance with the study protocol and procedures and how will the compliance of the local sites be monitored and reviewed? How will issues with compliance be remedied?

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