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NCT 972565-4

The Stony Brook University Calm-Mom Study

Study Protocol & Data Analysis Plan

3.2.1 RCT Methods. Potentially eligible participants from the OB research registry (NuPDQ ≥ 19 ; ≤ 20 weeks pregnant) will be contacted by our clinical research coordinator to schedule a baseline visit. All participants will undergo a full psychosocial evaluation (conducted by me or an MA level psychology intern) that will include a history of psychiatric and medical illnesses, a chart review, and the Structured Clinical Interview for DSM-5—Research Version (SCID-5-RV¹¹²) to assess current and past mental health. They will also complete a battery of computer administered self-report measures to assess mood symptoms, stress, anxiety, perceived social support and quality of life. At this visit participants will be randomized (as overseen by Dr. Schwartz, statistician on Advisory Committee) to either the SMART-Pregnancy program or TAU. A stratified randomization approach will be used. Strata will be based on medical pregnancy risk (high/low based on Prenatal Medical Risk Index (PMRI)⁶⁰ score) and psychotropic medication use. Participants randomized to SMART-Pregnancy will receive orientation to using Skype software and the project website. Participants randomized to TAU will receive a referral to the in-house clinical psychologist (located at the SBU Tech Park Clinics). The psychologist is available to see women as needed during their pregnancy. Patients from outside the SBU system (i.e., Winthrop or private practices) will be referred to low/no cost community providers such as the SBU Psychiatry Dept Residents' clinic (accepts medicare/Medicaid) or the Krasner Psychological Center (operates on sliding scale). SMART-Pregnancy group sessions will be conducted by myself and two trained advanced pre-doctoral interns under my supervision. Dr. Gonzalez (Advisory Committee) and I will monitor treatment fidelity following recommendations of the NIH Treatment Fidelity Workgroup¹¹³.

All groups will be delivered via Skype. Skype can be readily downloaded onto any mobile device (laptop, computer, or smartphone) and has been successfully used in prior and ongoing trials of SMART-based interventions¹⁰⁰. SMART-Pregnancy participants will be asked to complete a 5-10 minute online daily diary. As part of this diary, they will be asked to rate stress, mood, somatic, and anxiety symptoms and record daily practice of skills (e.g., relaxation, cognitive restructuring).

Participants in both groups will complete online, self-report questionnaires (taking ~ 20-30 min) at weeks 4 (mid-treatment), 9 (post-treatment), and 18 (10 week follow-up) and 6-weeks postpartum (see Table 2). Participants will be paid \$40 per major assessment time point and will be offered a bonus of \$20 for participating in all scheduled assessments. A research assistant will also monitor the EMR for participants with upcoming medical visits and coordinate with clinical staff to collect measures at the patient's visit. The combination of these methods has resulted in very high participant retention (90%+ at 6 month F/U) in previous treatment studies we conducted⁹⁸. A masked medical chart review will be conducted at baseline and after the participants' projected due date to assess birth outcomes and maternal health. Relevant chart notes will be extracted from the EMR and deidentified by a trained RA prior to data coding by myself and Drs. Garry/Sridhar.

Rationale for selection of TAU as comparator: We considered alternatives including a time/attention matched psychoeducational health enhancement program or support group. However, we ultimately selected TAU to maximize resources and trial feasibility. Considerations included pregnant women possibly not valuing a support group as highly as a skills group and the need to have a nurse present for health enhancement groups. We will compare pre-post treatment effect sizes

obtained for our intervention versus published effect sizes for other trials of CBT and mind-body interventions with pregnant populations to assess relative efficacy.

3.2.2 Assessments. See Table 3 for an overview of the timeline of assessments. Participants will complete a battery of self-report measures electronically to assess mood, quality of life,

social support, cognitive biases, mindfulness, health behaviors, and pregnancy-specific distress. We will utilize the NIH PROMIS computer adaptive tests (CATs) to assess these clinical outcomes¹¹⁴. At baseline, we will also assess demographic, smoking status, planned/unplanned pregnancy and alcohol use (control variables). Participants will have the option of completing the electronic assessments at home via a web-based link or at the clinic via an iPad. **Hair cortisol collection:** Participants will provide hair samples to

Table 2. Timeline of Assessments

Events	Week 0 (baseline)	Week 1-3	Week 4 (mid-treatment)	Week 5-8	Week 9 (post-treatment)	Week 18 (10 week F/U)	6-Weeks (Postpartum)
Clinical Interview	X						
Suicide Assessment	X		X		X	X	X
Daily Diary (SMART)		X	X	X			
Online Self-Reports	X		X		X	X	X
Hair Cortisol	X				X	X	
EMR Review	X					X	X

Table 3. Clinical Constructs and Self-Report Measures

Construct	Measure
Psychiatric Symptoms & Stress	
Depression	Patient Health Questionnaire – 9 item Scale (PHQ-9)
Anxiety	Generalized Anxiety Disorder – 7 Item Scale (GAD-7)
Perceived Stress	Perceived Stress Scale (PSS-10 ¹¹⁵)
Pregnancy Perceptions & Behaviors	
Prenatal Coping	Revised Prenatal Coping Inventory (NuPCI ⁹¹).
Prenatal Distress	Revised Prenatal Distress Questionnaire (NuPDQ ¹¹⁶).
Health Behaviors	The Prenatal Health Behavior Scale – Revised (PHBS ¹⁰⁴).
Maternal & Birth Outcomes	
Prenatal Maternal Health	Prenatal Medical Risk Index (PMRI) ⁶⁰ self-report+ EMR Review
Postnatal Maternal Health	ERM review: weight/height, blood pressure, medical visit attendance
Birth Outcomes	Delivery mode, birth weight %tile for gestational age, 5 min Apgar
Quality of Life	
Role Satisfaction	PROMIS V.2 Satisfaction with Participation in Social Roles & Activities
Global Life Satisfaction	Satisfaction with Life Scale (SWLS ¹¹⁷)
Social Support	
Perceived Support	PROMIS V.1 Emotional, Informational and Instrumental Support
Mindfulness, Coping & Cognition	
Mindfulness	Cognitive and Affective Mindfulness Scale (CAMS-R ¹¹⁸)
Stress Coping	Measure of Current Status (MOCS-A ¹¹⁹)

measure changes in cortisol levels, a method used successfully in prior studies⁶⁴⁻⁶⁶. Hair grows approximately 1cm/month, thus ensuring sufficient growth for collection. Participants will provide a hair sample for each of the 3 antenatal data collection periods. Samples will be provided at the antenatal medical visit occurring closest to the scheduled assessment date. Specifically, we will cut a small amount of hair (approximately 150 strands or the density of a small paperclip) as close to the scalp as possible (about 3 cm), and from the back of their head. **Rationale for hair cortisol vs salivary cortisol:** Hair cortisol has been validated as a measure of long-term integrated free cortisol production that correlates with traditional salivary cortisol measures¹²¹. Hair cortisol provides a more complete snapshot of cortisol concentration levels across long periods (e.g., over the past 2 months) whereas salivary cortisol captures more acute responses to stress¹²². As such, studies have been more likely to find changes in hair cortisol levels in response to stress interventions¹²³. Hair cortisol collection is feasible in pregnant populations, is correlated with perceived stress^{124,125} and has been validated against salivary cortisol^{101,126}. Hair sample collection is less invasive and easier to collect/store than saliva sampling. Shipping/Processing: Hair cortisol concentrations (HCC) will be processed by Dr. Jerrold Meyer's (advisor committee) laboratory at the University of Massachusetts, Amherst. Samples will be labeled and stored at room temp prior to shipping.

3.2.3 Primary Outcome. 1) Feasibility: We will evaluate intervention feasibility by rates of study eligibility (% of referred patients who are eligible), enrollment (% of eligible pool who enroll) and retention through 6-weeks postpartum (i.e., completion of all 3 follow-ups). Feasibility metrics for the daily diary and hair sampling will include average days with diary entries, completeness of entries and HCC collection rates.

3.2.4 Secondary Outcomes. Secondary outcomes will include treatment engagement, acceptability and preliminary efficacy. We will assess engagement as retention mean number of treatment sessions completed per participant. The Credibility and Expectancy Questionnaire¹²⁷, a validated five-item scale measuring expectancies for treatment outcomes, will be administered following Session 1. We will also assess acceptability following completion of the trial via Likert-type and open-ended questions. Items will assess program: 1) enjoyability, 2) helpfulness, 3) relevance and 4) convenience. Satisfaction with treatment: 1) structure, 2) timing (i.e., early v later in pregnancy) and 3) content will also be assessed. Preliminary efficacy outcomes will include maternal mental health symptoms (depression, anxiety, anger and stress) and birth outcomes as extracted from EMR chart review (verified by maternal self-report). Dr. Garry and I will use the Prenatal Medical Risk Index (PMRI)⁶⁰ to develop a data coding and extraction plan for prenatal health data and pregnancy risk. Maternal health variables assessed will include preeclampsia, weight gain (following IOM guidelines¹²⁸), diabetes (gestational or pre-existing), anemia, flu syndrome, genito-urinary infections, incompetent cervix, substance abuse, tobacco use, placenta previa, postmaturity, threatened abortion and, 2nd

or 3rd trimester bleeding. Labor/delivery outcomes of interest will include mode of delivery (cesarean section), birth weight < 10th or >90th percentile for gestational age, 5 min Apgar score < 7¹²⁹. We will also explore possible mediators of treatment outcomes in the SMART-Pregnancy group (i.e., birth outcomes and maternal mental health) including: coping skills, social support, health behaviors and HCC.

3.7 Data Analyses.

3.7.1 Preliminary Analysis. Descriptive statistics, including means and standard deviations, will be calculated for all study variables. The distributions of the residuals for these variables will be assessed for normality. Scale scores will be evaluated for internal consistency and variability. Bivariate correlation tables will also be examined for redundancies among variables and for associations with demographic variables.

3.7.2 Main Analysis. Feasibility analyses will be conducted in SPSS v.23. I will be responsible for all data cleaning and preliminary analyses. I will conduct final analyses under the supervision of Dr. Schwartz. Descriptive statistics, including means, frequencies, and ranges will be used to describe the sample and to summarize feasibility. Participants who complete all three F/U assessments will be identified as “program completers”. Response frequencies will be calculated to identify reasons for ineligibility and enrollment refusal. We will also compute odds ratio for program completion (i.e., retention) by group.

3.7.3 Secondary Analyses. Secondary analyses will be conducted in SAS 9.4. Maternal mental health outcomes will be examined via a multilevel modeling (MLM) approach using the PROC MIXED command with restricted maximum likelihood estimation¹³⁰. All tests will set Type I error rate to 0.05 and consider two-sided alternatives. For the longitudinal growth models separate models will be constructed for each outcome of interest (i.e., maternal stress, depression, anxiety and anger) using 7 time points. For all analyses we will use a model building approach. First, we will test effects of the target variables at baseline and demographic covariates (e.g., SES, prenatal OB-risk assessed via the PMRI⁶⁰) on each target outcome. To conserve power, we will remove variables that do not significantly predict the target, as indicated by the likelihood ratio test (LRT)¹³¹. Finally, treatment condition (SMART vs TAU) will be added to the model. We will also examine of non-linear and piecewise models to account for discontinuities in outcome variables.

An ANCOVA-based approach (PROC GLM) will be used to investigate birth outcomes across groups. We will also evaluate whether any observed effects of intervention (SMART vs TAU) on birth outcomes are mediated by changes in the theoretical treatment targets: maternal stress modulation (i.e. HCC), health behaviors or stress coping skills. Residualized change scores will be computed for each putative mediator. Next we will evaluate the indirect effect of treatment condition on birth outcome through the hypothesized mediators using a structural equation modeling approach (SEM) in AMOS 24.0. SEM combines linear regression and factor analysis to map the paths between observed and latent variables and the associated error terms¹³². All relative and total indirect effects will be subjected to follow-up bootstrap analyses with 10,000 samples¹³³ and 95-percentile CIs will be derived^{134,135}.

Statistical Power. The sample size is powered for the primary outcome, feasibility. Feasibility is defined as the percentage of participants across both study arms who complete all 3 scheduled follow ups. Previous trials of the SMART program delivered online in other populations have produced excellent study completion rates (80-100%^{100,136}). Thus, we have conservatively selected a study completion benchmark of 75%. With a total sample size of $N = 60$, we will be able to estimate a study completion rate of 75% to within a 95% confidence interval of +/- 10%. With regards to estimating an effect size for calculating power in future RCTs (secondary aim), the literature suggests that a minimum total sample size between 24 and 50 participants is recommended for powering pilot trials to maximize accuracy of effect size estimation and minimize resource allocation¹³⁷⁻¹⁴⁰. Thus, a total $N = 60$ ($n = 30$ SMART pregnancy, $n = 30$ TAU) should be ample.