Promoting Self-Management of Breast and Nipple Pain with Biomarkers and Technology (*PROMPT*) for Breastfeeding Women study (1 R01 NR020041-01) RCT

Purpose/Introduction:

Every year, 1 million women cease breastfeeding (BF) before 6 months, the minimum time required for optimal maternal well-being and to promote their infant's health, physical growth, and development.[1–3] The highest rate of BF cessation occurs within 3 weeks after delivery, with 30% of women ceasing BF due to acute breast and nipple pain (BNP).[4–6] BNP is a complex and understudied biobehavioral phenomenon involving nociceptive signaling that stimulates multiple pathways - somatic (mechanical compression and cracked nipples), visceral (uterine cramping), and the autonomic nervous system (engorgement).[7–10] Enhanced pain sensitivity, a physiologic pro-nociceptive state measured by somatosensory function and genomics, may increase women's sensitivity to BNP.[10,11] Women who experience BNP beyond BF initiation *report lower BF self-efficacy a key predictor of BF at 6 months,* and increased symptoms of maternal distress (anxiety, depression, stress, and fatigue), which contribute to a greater risk of early BF cessation (< 3 weeks BF), decreased maternal well-being, and low maternal self-efficacy to care for their infant.[12–15] Thus, a critical gap exists in identifying effective biobehavioral self-management interventions for women during BF initiation to manage BNP, increase BF self-efficacy, BF duration and decrease symptoms of maternal distress.[16–19]

In a pilot RCT (P20NR016605 - UConn IRB #H16-321)), we developed a patient-informed **B**reastfeeding and **B**NP **S**elf-**M**anagement **(*BSM*)** intervention based on the Individual and Family Self-Management Theory and tested its feasibility among women initiating BF.[20–22] The *BSM* intervention was designed to address modifiable variables for women initiating BF.[23–26] Based on the needs and preferences elicited from a diverse sample of BF women, we used a cloud-based platform, to deliver BF knowledge and skills, and provided support through nurse led text-based communication to decrease BNP, increase BF self-efficacy, and increase adaptive coping behaviors.[27–30] The RCT pilot was successful, with 92% retention and 87% of women continued BF until study end.[22] Women in the *BSM* intervention group with and without prior BF experience reported significantly reduced BNP intensity and pain interference at 1 and 2 weeks which predicted increased BF self-efficacy and decreased anxiety at 6 weeks. BNP intensity was associated with pain sensitivity single nucleotide polymorphisms (SNPs) (Oxytocin receptor (*OXTR)* rs53576, rs2254298), suggesting a genetic risk profile of heightened BNP and linked to perinatal depression (*OXTR* DNA methylation) which together could be used to identify women at high risk of early BF cessation and pain sensitivity.[22,31–36] Our innovative pilot study was the first to address BNP using the *BSM* intervention. In this application, we propose a large-scale RCT to further test the efficacy of the intervention on BNP, BF self-efficacy, maternal well-being, and BF exclusivity to 6 months.[22]

Based on our promising preliminary data, we propose to examine the effectiveness of the *BSM* intervention in an R01 RCT, ***Prom****oting Self-Management of Breast and Nipple* ***P****ain with Biomarkers and* ***T****echnology* ***(PROMPT)*** *for Breastfeeding Women*, on BNP and BF outcomes (exclusivity and duration). Women (N=280) will be randomized to the *BSM* intervention or an attention control (general postpartum and infant care) group. At baseline, women will be assessed for BNP intensity and interference, and contextual factors of *BSM* (pain sensitization using quantitative sensory testing, buccal cell and/or blood samples ((2) 5 ml EDTA tubes and (2) 2.5 ml DNA/RNA tubes (15 ml or 3 teaspoons) at each visit for total of 9 teaspoons) for select pain sensitivity and milk supply SNPs and DNA methylation). After initiation of the intervention, women will be assessed at 1, 2, 3, 6, 9, 12, 18, and 24 weeks for BNP, BF exclusivity, BF self-efficacy, maternal well-being, and at **6 and 24 weeks** for DNA methylation of pain and milk supply and ongoing pain sensitization. The specific aims (SA) and hypotheses (H) of the ***PROMPT*** study are to:

SA1: Examine the effect of the *BSM* intervention on the primary outcome of BNP intensity and interference between the intervention and attention control group controlling for prior BF experience across all data points.

H1: The *BSM* group will report significantly lower BNP intensity and interference at 1, 2, and 3 weeks and significantly lower cumulative BNP score over time compared to the AC group.
SA2: Examine the effect of the *BSM* intervention on secondary outcomes of BF exclusivity, BF self-efficacy, and maternal well-being.
H2A: The *BSM* group will have a higher proportion of women with exclusive BF at 6, 9, 12, 18, and 24 weeks and higher BF self-efficacy at all-time points compared to the attention control group. **H2B:** The *BSM* group will have higher maternal well-being compared to the attention control group at each time point.
SA3: Explore (1) the influence of pain sensitivity (quantitative sensory testing, select buccal cell and/or blood samples for pain sensitivity SNPs and in a subsample, DNA methylation of select sensitivity SNPs (40 participants (5 zero and 15 highest pain phenotype per group) on BNP intensity and interference; and (2) BF outcomes in SA2, maternal and pain self-efficacy over time between groups.
SA4: Explore (1) the influence of pain sensitivity and lactation (blood samples for pain sensitivity and lactation SNPs [*OXTR* and *PRL*]) on perception of milk supply (BSES and HH lactation scale).

Aligned with the Maternal and Infant Care goals of Healthy People 2020, NINR strategic themes of symptom science and self-management, NICHD optimal infant and maternal heath during the fourth trimester, and the CDC *HEAR HER* campaign, the proposed study will address a major barrier to BF initiation and exclusivity by testing the effectiveness of the *BSM* intervention to decrease BNP intensity and interference and increase BF self-efficacy and support maternal well-being. The *BSM* intervention is easily accessible and clinically sustainable allowing for large-scale translation in health care and public health settings.

Significance

Exclusive BF is defined as infants receiving only breast milk from the breast or from expressed breast milk

A key preventative health behavior for lifelong health is breastfeeding.[1] Women who reported a cumulative breastfeeding (BF) history of 12 months or more decrease their risk for breast cancer and cardiovascular disease.[1,3,37] BF supports maternal well-being during the fourth trimester of pregnancy after birth by decreasing the risk of depression, anxiety, and stress symptoms, and increases maternal self-efficacy.[38–43] BF also provides lifelong infant health benefits; the longer infants **exclusively BF**, the greater benefit in reducing infantile and respiratory diseases (COVID-19), and chronic diseases related to obesity.[2,44,45] In 2019, 83.2% of women-initiated BF, unfortunately, **3 weeks after birth the rate of exclusive BF dropped to 62% triggered by breast and nipple pain (BNP),**[4,6,19,46–49] **thus, BF health benefits for women and infants are lost**.[1,2] The public health goal to receive optimal health benefits from BF is 6 months of BF, which requires women to maintain their milk supply **for at least 9 weeks**.[50] The early cessation of BF (before 3 weeks) costs society an estimated $3.0 billion annually (2010 dollars) due to purchase of formula, increased infantile diseases and health visits, and lost wages ($2.3 billion being maternal cost).[2,51]

BNP leads to BF cessation. Clinically, BNP during BF initiation is managed as a "normal" phenomenon that women experience.[8,52] For women who experience unresolved BNP during BF, BNP triggers a complex feedback loop which creates a challenging situation that includes stimulation from the glandular, somatic, and visceral tissues, which is transmitted via nociceptors pathways.[10,53,54] During the critical **2-3 weeks of BF**, women will continue BF with BNP, to provide optimal nutrition and build their maternal self-efficacy, detrimentally, for each day of ongoing BNP, the risk of BF cessation increases by 10-26%.[19,48,55–57] Common triggers of BNP are related to anatomic factors, such as abnormal nipple shape, pumping, and ankyloglossia, or an infectious process. These triggers may be resolved with guided BF interventions and treatment.[58–63] However, without resolution, 30% of women (1 million) cease BF early due o*ngoing BNP* which disrupts the neurohormonal cascade of lactation triggering *inadequate milk volume* and a *lack of*

infant satiation.[6,9,19,34,35,46,47,64–67] At 1 and 3 months, 20 – 30% and 16% of women, respectively, experience ongoing pain even with professional lactation intervention. [68–70] The persistence of pain without medical conditions or anatomic anomalies suggests a genetic risk of pain sensitivity and insufficient milk supply.[10,31,36,71,72] A **genetic risk of enhanced pain sensitivity** may be used to identify women at high-risk for pain-related BF cessation and target precision interventions for BNP and also be a pathway to identifying women at risk for chronic pain due to a pain sensitivity phenotype.[11,31]

Based on the voluminous evidence regarding the effectiveness of pain-specific, non-pharmacological self-management strategies, **the *scientific premise of this application*** is to provide knowledge and skills at BF initiation to prevent BNP, increase coping mechanism and change behaviors if BNP occurs.[8,10,73–77] Cognitive-behavioral and self-management interventions directed at clinical and chronic pain conditions (guided imagery, therapeutic breathing, mindfulness, relaxation, use and safety of analgesics have not been applied BNP to facilitate BF exclusivity and duration.[8,10,73–80] A key consideration for women with ongoing BNP (≥2 weeks) is that similar to women with chronic pain conditions,[77,81–84] women are at greater risk for alterations in self-efficacy, mood disturbances, activities of daily living, and in sleep cycles affecting their general well-being.[54,85–90] Decreased maternal well-being adversely affects maternal self-efficacy with enduring and negative impact on the maternal/infant dyad and typical infant growth and development.[12,15,19,66,91,92] To address both the lack of theoretically driven content for integration of Breastfeeding and BNP self-management, lack of maternal strategies regarding BNP, and issues of intervention sustainability in the clinical setting, our team employed user-centered design methodology to develop the **B**reastfeeding and **B**NP **S**elf-**M**anagement (*BSM)* intervention.[21,93,94] This process involved gathering information through personal interviews and focus groups of women who had current or past histories of BF regarding their needs and preferences for the *BSM* intervention, their value specifications and methods of delivery.[19,93,95] The *BSM* intervention entailed an **electronic journal for monitoring BF and BNP with feedings, bi-weekly texting** for 6 weeks from a research nurse for informational support and to promote personalized goal setting and problem-solving, hyperlinks to **uniform BNP educational modules** (knowledge and skills) and online resources.[21,96]

Individual and Family Self-Management of BNP. In an NINR funded pilot RCT study (P20NR016605), our research team guided by the Individual & Family Self-Management Theory innovatively utilized the *BSM* intervention. The Individual & Family Self-Management Theory conceptualizes self-management as a process in which women use knowledge, beliefs, self-regulation skills and abilities and social facilitation to manage their BNP and achieve BF goals (Figure 1). Self-management occurs in the context of risk and protective factors specific to BF, including pain sensitization, frequency of pain specific SNPs, the physical and social environment, and individual and family factors. Using self-management process factors of knowledge, and beliefs (pain, BF, and maternal self-efficacy), self-regulation skills and abilities (latching, positioning, nipple care, identifying signs of *Candida* or *Staph* infection), and social facilitation to achieve health-related outcomes.[75,76] Pain self-management is pivotal to women's BF success as measured by the proximal and distal outcomes. Proximal outcomes are acute and cumulative BNP intensity and interference and BF duration, use of analgesics and non-pharmacological therapies, and maternal well-being (anxiety, fatigue, depressive, and stress symptoms). Distal outcomes are related to the success of the proximal outcomes and include exclusivity and duration of BF, and perceived well-being. These outcomes meet the recommendations of optimal maternal health during the fourth trimester of pregnancy and maternal-infant health goals by national and clinical agencies.[45,85,87,97–100] Our structured theory driven *BSM* intervention targets self-management process factors especially during the 2-3 weeks of BF initiation when women value affirmation and guidance,[18,48,101] and knowledge and skills to manage BNP.[25,26,74,102,103]

BSM intervention utilizes proven interventions for BF self-efficacy and BF duration. BF self-efficacy educational interventions provide **standardized and best practice** knowledge and skills to facilitate positive thoughts and maternal self-efficacy for BF exclusivity.[104–106] Women who received antenatal BF education, Baby-Friendly Ten Steps based lactation support after delivery and have multiple contact points (4 to 8 targeted structured interventions) using BF journals, web-based or face-to-face interactions reported greater BF self-efficacy, decreased depressive symptoms and fatigue, and higher BF rates at 1 and 2 months.[25,26,107–112] These interventions are effective if best practice is followed,[113] but costly and difficult to integrate into the fourth trimester care of women in the clinical or public health setting, thus wider dissemination outside of clinical trials has been limited.[114,115] A less intensive but effective intervention for women of child-bearing age and in diverse populations is text-based communication, which targets BF education.[28,30,114] However, although effective, these BF self-efficacy interventions have not addressed women's daily experience of BNP with BF or the presence of ongoing postpartum pain.[13,18,30,101,112] BF interventions have also ignored BNP and BNP molecular risk as a pathway to self-efficacy, increased BF self-efficacy scores are related to decreased report of BNP.[19,72] Women are clear that with increased pain, there is a decrease in BF self-efficacy and a higher rate of early BF cessation.[6,19] Our intervention innovatively targets BNP self-management as a pathway to build self -efficacy and addresses a critical need of women at home through text-based communication and cloud
based modules.

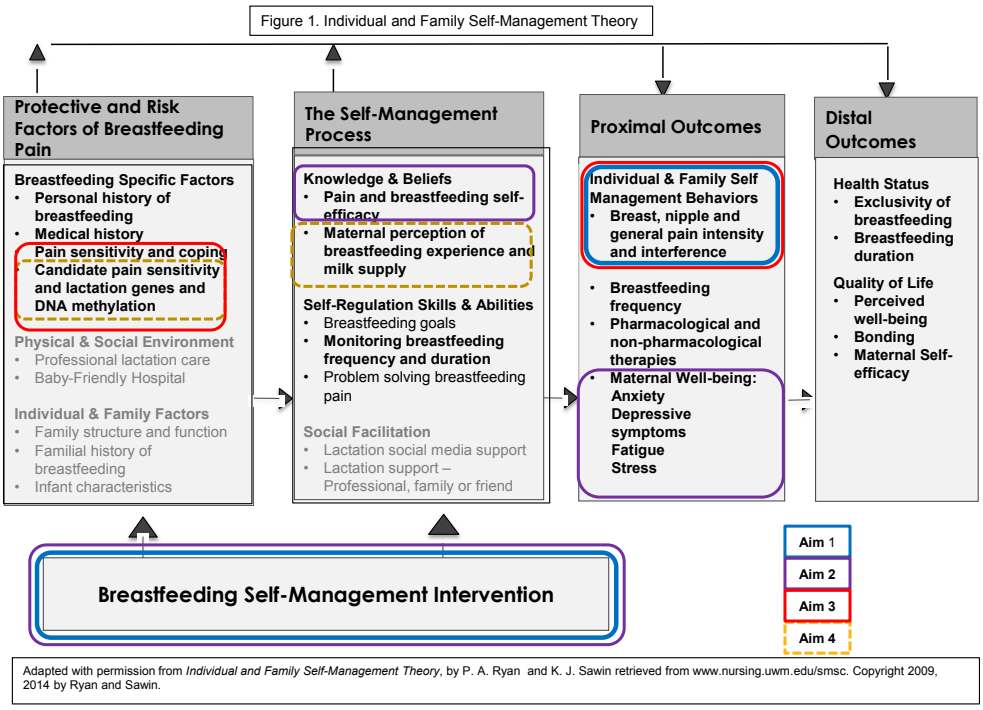

Figure 1. Individual and Family Self-Management Theory for BNP

Pilot study results from our research team.[22] The pilot study lasted 6 weeks with 83% of the eligible women approached consented and mirrored the Connecticut diversity population.[4,22,116] Women were excluded with a risk of altered pain sensorium such as a chronic medical condition or taking prescription medications. Women were randomized by age and delivery, and 92% of women provided data at baseline, 1, 2, and 6 weeks. At 6 weeks, 87% of women were BF compared to the national average of 79%, with no significant difference in diversity or parity.[4] Women randomized to the *BSM* intervention, compared with the attention group, reported significantly decreased BNP at 1 and 2 weeks; decreased pain interference scores at 1 week predicted increased BF self-efficacy scores and increased BF self-efficacy scores positively correlated with exclusive BF at 6 weeks.[22] At week 6, increased BF self-efficacy scores significantly predicted maternal well-being outcomes of anxiety and sleep disturbances, aligning with the literature.[22,29,86,117–120] **The proposed study will build on our strong pilot results and extend the**

outcome measures to 24 weeks. We anticipate that compared to the attention control group, the *BSM* intervention group will increase BNP and general body pain management, reduce BNP intensity and interference, and exceed national BF exclusivity rates at 6, 9, 12, 18 and 24 weeks. We postulate that decreasing BNP will increase BF self-efficacy, maternal well-being, and maternal self-efficacy to care for their infant.[12,15,72,121] The proposed study will explore the occurrence of BNP beyond BF initiation, and barriers to BF including maternal return to work and sustaining milk supply by pumping.

Rationale to target biobehavioral mechanisms of BNP in the self-management intervention. It is logical that a subset of women experiences greater levels of pain intensity based on the presence of genetic polymorphisms of pain sensitivity genes (risk alleles),14 however, this **has not been systematically studied** in BNP during BF. Genetic risk factors (pain sensitivity single nucleotide polymorphism (SNPs)) increase vulnerability to peripheral and central pain sensitization and increase the likelihood of early BF cessation.[10,11,122,123] Oxytocin receptor gene (*OXTR*) is emerging as having a moderating role in pain sensitivity and pivotal to maternal milk supply.[9,36,124–126] In our pilot study, women with an *OXTR* SNP minor allele (rs53576), and not catechol-o-methyltransferase *(COMT)* alleles reported increased mechanical pain sensitivity at baseline, and experienced significantly greater BNP at two weeks, and those with minor allele rs2254298 were more likely to experience allodynia.[31] The presence of the minor allele relationship to increased pain may have an indirect effect on duration of labor, breast milk supply, and BF exclusivity.[9,64,122] In addition, differences in the DNA methylation of *OXTR* rs53576 are predictive of postpartum depression, social attachment, and psychological resources across the lifespan.[32,127–129] The proposed study will build on the pilot RCT exploration of the effect of *COMT* and *OXTR* SNPs on BNP, BF and response to the *BSM* intervention and explore a subset of 40 participants (5 zero and 15 highest pain phenotype per group) whole genome bisulfite sequencing (WGBS) to evaluate DNA methylation of within *COMT*, *OXTR,* and other pain genes based on preliminary evidence of differential expression associated with a specific pain phenotype. [32,36,130,131] In addition to providing high quality data to explore a BNP phenotype, WGBS also provides the opportunity to explore the methylation status of OXTR, PRL and PRLR and to evaluate methylation for adequate maternal milk supply. So, while the present study will assess only some of the data produced by WGBS, the addition of OXTR, PRL and PRLR DNA methylation will provide a useful source of data for subsequent hypothesis testing and hypothesis generation connecting pain sensitivity to maternal milk supply (Please see amendments of Amoo ISONG grant and Lucas UConn grant).[36,132,133] Therefore, **the integrated approach we have taken in the design of the *BSM* is supported by previous research findings, as well as our pilot study**.

Somatosensory measurement of pain sensitivity and BNP. Extending these findings, our pilot study showed **that peripheral and central sensitivity of BNP may be objectively measured using somatosensory quantitative sensory testing.**[31] By characterizing each woman's pain sensitivity profile and intrinsic ability to dampen pain (conditioned pain modulation), we may be able to determine the precise mechanisms affected by the selected risk alleles. Moreover, these data will contribute to an objective understanding of pain variability in women who are initiating BF, and the influence of pain self-management on BNP.[134] **In our pilot study, we found women reported greater sensitivity to mechanical pressure similar to women with breast cancer pain**.[31,135,136] Women in our pilot RCT with greater sensitivity reported higher levels of pain interference, pain sensitivity and was predictive of BNP at 1 and 2 weeks. To date, only one case study evaluated somatosensory pain sensitivity using mechanical pain thresholds and found women with increased breast tissue pain sensitivity had an increased risk of chronic pain.[71] Ongoing BNP with BNP sensitivity may potentially influence future risk of comorbid pain disorders and chronic pain.[71,137–139] Quantitative sensory testing will examine pain sensitivity as an important contextual factor of pain self-management within 48 hours after birth, at 6 weeks when postpartum discomfort has resolved and at 6 months to assess the effect of the BSM intervention.

Implications for women's pain across the lifespan. Although BNP has not been recognized as a formal "pain" condition,[74,139] it is considered to be high impact because BNP can interfere with BF outcomes, persist throughout the postpartum period, affect maternal well-being and affect the lifelong health of women and infants.[2,3,15,140,141] In our pilot study, women in the control group reported significantly higher BNP cumulative pain and anxiety at all data points which affects pain perception as seen in other clinical pain conditions.[141–147] Of concern is that women over their lifetime, experience greater pain sensitivity than men and are predisposed to clinical and chronic pain conditions.[74,148] This variation in pain experience is complex and related to pain sensitivity, genomic factors, psychological and social well-being but has not been connected to BNP.[11,32,134,148,149] Together, women are more at risk for chronic pain conditions and increased use of opioids, with perinatal women considered a vulnerable population requiring additional clinical oversight during the fourth trimester.[74,85,99,150]

The rationale for the timing of data collection at baseline, 1, 2, 3, 6, 9, 12, 18, and 24 weeks. In the proposed RCT, the *BSM* intervention will begin the first week after birth, when women shelter at home to BF, and have access to a smart phone, thus providing women with standardized and best practice BF and BNP problem-solving skills during an acute period of pain when the rate of BF cessation is the highest.[15,113] In our pilot study, we found statistically significant and clinically meaningful differences in *pain intensity* at 1 and 2 weeks and *pain interference* as predictive of BF self-efficacy at 6 weeks between groups, especially among women with increased pain sensitivity at baseline.[22] Thus, the second and third weeks are an important period for assessing the length of time needed for the *BSM* intervention to support the women's use of knowledge and skills for BNP self-management and its impact on proximal and distal outcomes. The 6, 9-, 12-, 18-, and 24-weeks data points will allow us to extend our study, explore the effect of the intervention on maternal well-being, and DNA methylation of pain sensitivity SNPs on decreased BNP and BF exclusivity. All of the data points (baseline, 1, 2, 3, 6, 9, 12, 18, and 24 weeks) align with the national BF duration metrics and the duration of BF recommended by clinical agencies (WHO, CDC, ACOG, AAP, AWHONN).[4,45,100,151] These nine data points will allow us to describe the impact of the *BSM* intervention on women's BNP intensity and interference, the risk of early BF cessation, the occurrence of BNP after BF initiation and the risk profile of acute to chronic pain.

Innovation

The proposed project is innovative in the following respects:
1) Our study will be the **first** to test a theoretically based BF and pain self-management intervention designed for women experiencing BNP during the critical first weeks of BF initiation. The assessments of pain intensity, pain interference and pain sensitivity in BF women, as well as the intervention components, are aligned with the biopsychosocial model of pain, one of the most widely cited models for understanding the cogent variables that influence pain perception and pain outcomes.[75,152]
2) The proposed study is novel for lactation science to measure the biobehavioral variables that affect BF outcomes including measurement of pain sensitivity using quantitative sensory testing and pain genomics (selected pain sensitivity SNPs and DNA methylation), influence on BF exclusivity.
3) The intervention delivery platform uses a patient-centered approach based on user needs (information) and preferences (texting) for incorporating the intervention into their daily lives.[153,154] The project targets the critical window of 1-3 weeks after BF initiation when BNP and BF cessation risk is highest.[6,47]
4) The delivery of the intervention is via mobile technology accessible to women in their home, during the time of BF initiation when support is most valued and in which face-to-face visits are most burdensome and places the mother-infant dyad at risk for illness, such as COVID-19.[28,101,154]
5) The ***PROMPT*** study novelty is using the *BSM* intervention to identify the personal risk and protective factors of BNP, which holds great promise for 1) precision interventions for BNP, as well as the replication and extension of our pilot study findings with pain sensitivity polymorphisms (*COMT*, *OXTR*) and DNA methylation roles in BF pain and maternal well-being, and the development of easily accessible

strategies for women BF within clinical settings that allow for large-scale translation in health care systems and public health settings.

Approach

To examine the efficacy of the *BSM* intervention in BF women on BNP intensity and interference and BF outcomes, we have designed an RCT with two groups: the *BSM* intervention and attention control group. An attention control group was selected to control the influence of daily reflection and bi-weekly attention for participants in the *BSM* intervention group.[155] The self-management measures of the study were selected based on the Individual & Family Self-Management Theory pilot work by the PI regarding management of BF. Our team includes **Drs. Lucas (PI), Henderson, and Walsh** collaborated on the design of the longitudinal intervention based on their expertise in conducting longitudinal studies with maternal-infant populations.[22,31,156] Dr. Henderson is an expert in **maternal child health and with genomic, clinical, and translational methods** that are predictive of pain phenotypes. Dr. Steve Walsh, statistician, is an expert related to **study design, data collection, data management, and statistical analysis**. **Dr. Young**, geneticist at the University of Kansas Medical Center, is a long-time collaborator and is an expert in quantitative sensory testing in human subjects, **molecular/genetics methodologies** and design/implementation/statistical analyses of behavioral and **genetic data on the molecular genetics of pain**.[31,157,158] Dr. Lucas, together with the Co-Is developed the current and evolving exploration of BF and BNP as a biobehavioral phenomenon.[21,22,31] In particular, Dr. Lucas' pilot work (P20NR016605) tested the feasibility of the *BSM* intervention in several clinical settings with long standing relationships. The research and clinical team bring together the experience needed and through bi-weekly meetings which transitions to weekly meetings in which Dr. Lucas will provide oversight of study milestones. The proposed ***PROMPT*** **RCT** expands the PI's pilot study to test the *BSM* intervention in a larger sample for efficacy testing.

There are three sub study attachments that explore additional questions based the data collection. The first attachment is the Lucas Seed Grant OXTR and Maternal milk supply which with additional funding, will explore the relationship of DNA methylation of OXTR in pain insensitivity and maternal milk supply (see funded grant attachment). A second amendment is for Tumilara Amoo, graduate student at UConn School of Nursing and key personnel on the study, who will explore the role of prolactin receptors related to milk insufficiency for her funded dissertation (see ISONG funded grant and attachment). The third attachment is for Rachel Hage, key personnel on the study and honors student at UConn, will use the 6- and 24 – week interviews to explore how text-linked modules on infant development help maternal self-efficacy in taking care of their infant children.

1. Preliminary Studies

1.1. Recruitment and retention of women initiating BF. Dr. Lucas has conducted biobehavioral studies of BF using multiple methods. Dr. Lucas adjusted the number of women approached to fulfill the planned enrollment based on infant gestation and study burden.[159] For telephone and the text-based study designs, a **10 – 20% increase of the planned enrollment** met the sample size with a 90% retention of participants at 4 weeks with peak attrition at 2 weeks.[156,160] Videotaping preterm and full-term infants BF and testing a BF diagnostic device prototype in the home required a **100% increase** of the planned enrollment with an 80 – 85% retention of participants at 4 weeks and peak attrition after 1 week.[95,161] The pilot RCT used text communication, email, telephone contact and increasing monetary incentives to retain 94% of participants with peak attrition in 1 week.[22]

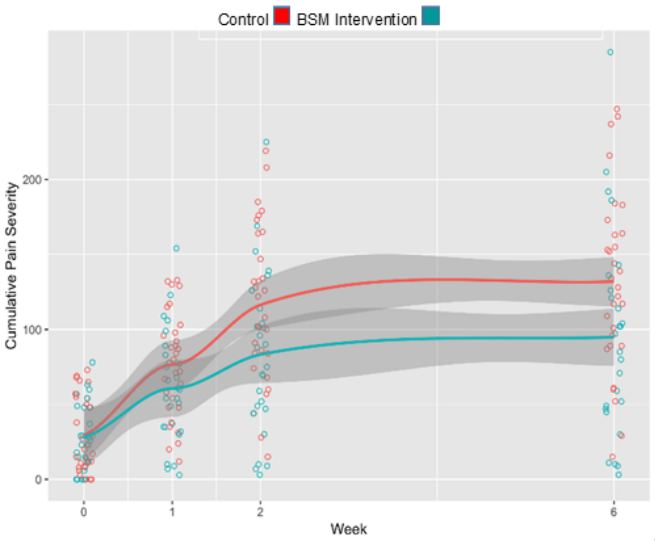

Figure 2. Cumulative BNP at 1, 2, and 6 Weeks Using a Visual Analogue Scale (0 - 100)

1.2. Randomized control trial using the *BSM* Intervention to decrease BNP. The PI completed an RCT pilot study (P20NR016605, PI: Starkweather) to test the feasibility of the *BSM* intervention on pain intensity and BF frequency and BF exclusivity and to identify somatosensory and genetic factors that place women at risk for BNP phenotype.[22,31] Our team conducted the pilot RCT at two clinical sites within **four months** including on-site data collection, web-based data entry, and follow-up text-based communication with participants (n = 65) resulting in a 94% participation retention rate.[21,22] The *BSM* intervention group reported significantly lower BNP using a visual analogue scale (0 - 100) at 1 and 2 weeks. Participants' cumulative BNP (baseline +1 week, + 2 week, + 6 week, 0 - 400) was significantly different between groups at weeks 1, 2, and 6 (Figure 2). Higher Brief Pain Inventory interference scores at 1 week was predictive of increased BF self-efficacy scores at weeks 1, 2, and 6. Aligning with the literature BF self-efficacy scores correlated with BF exclusivity and at 6 weeks significantly predicted maternal well-being symptoms.[29,86,117] Women experienced **an 8.18 increase in BF and BNP scores over time with the minor allele A of rs53576 (Figure 3)**. The somatosensory testing results also showed that for every 1-unit increase in the Mechanical Detection Threshold test, women experienced 16.51 higher BNP scores and 4.82 higher BNP scores for the Windup Ratio. Six women with the *OXTR* rs2254298 minor allele experienced allodynia sensitivity.[31] <u>These risk factors will be examined in the larger study to determine replicability</u>. <u>The effect of the components of the *BSM* intervention on BNP were examined independently without significance which demonstrates the importance of a multifactorial approach.</u> Participants' feedback of the *BSM* intervention included that texting was helpful while the paper-based daily journal was burdensome. All participants reported that the weekly survey completion was not burdensome.

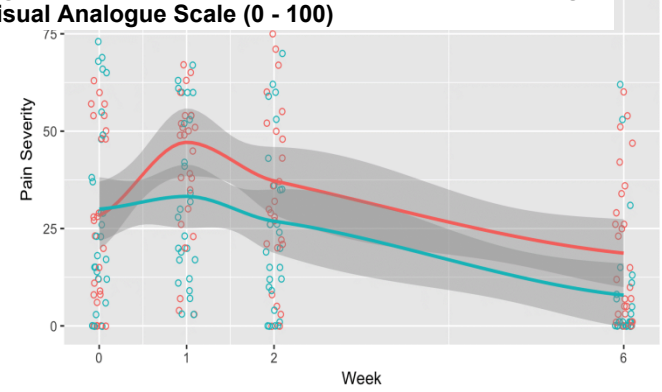

Figure 3. BNP for *OXTR rs53576*

1.3. Maternal Assessment of Infant BF Behaviors. Over 4 weeks, 115 BF women (38 late preterm and 77 full term) described their infants' BF behaviors which the PI analyzed using a breastfeeding

algorithm[162,163] and coded video recordings of a subsample of 27 infants (7 late preterm and 20 full term) jaw movements during BF. Using logistic discriminant analysis, 4 clusters of BF behaviors were identified (under preparation).

Together, the preliminary work provides evidence of the PI's ability to recruit and retain women in longitudinal studies that examine BF biobehaviors and to test the *BSM* intervention, as well as her motivation and dedication to maintaining a productive program of research. For this proposal both data collection and analysis will be facilitated by the contributions of her Co-Is. The University of Connecticut School of Nursing (UConn SON) offers a supportive environment for Dr. Lucas to carry out the study, including reserved laboratory space and portable equipment. Her solid collaborations with the study sites will ensure ample enrollment of a diverse sample of women, with efficient attainment of study milestones and dissemination of findings.

Participant Population

The sample size objective for the study is to recruit N = 280 women who will be randomly assigned to the *BSM* or attention control study groups at a 1:1 ratio (140 per group). The *BSM* intervention is designed for all women who initiate BF since both primiparas, and multiparas are affected (naivety or anticipatory based on prior BF experience) by some degree of pain.[19,43,56,68,164] As it is not possible at this time to identify women at risk of early BF cessation due to pain or enhanced pain sensitivity, it is expected that the higher number of women in the *BSM* group will continue BF over the study duration.

Enrollment and Randomization

After informed consent and prior to the start of data collection, the participants will be randomized to the *BSM* intervention or the attention control group and be assigned a unique participant identification number (PID#). The sample size objective for the study is to recruit N = 280 women who will be randomly assigned to the BSM or attention control study groups at a 1:1 ratio (140 per group). Random assignment will be performed using an established dynamic minimization algorithm, proposed by Pocock and Simon [165] . The algorithm is implemented thru an R package called "minirand", developed by Jin et al. [166]. The interactive tool is developed as an R shiny app embedded in REDCap. This technique will maintain the 1:1 ratio between participants assigned to the BSM and control conditions, but will also ensure that participant characteristics that are known to be predictive of breastfeeding outcomes will each be balanced across the study groups. Those predictive characteristics include: age, race, breastfeeding experience, expected breastfeeding duration, route of delivery, and intent to return to work.

The reason we choose this algorithm is the complexity of the randomization needed for our study. With 280 expected participants and 6 stratifying characteristics, the simple randomization may not yield a balanced arm assignment in every allocation. However, the dynamic feature of our randomization will incorporate both the existing assignments and the imbalance at each level of the stratifying characteristics and assign the next participant to minimize the overall imbalance. With the large number of total enrollments in our study, this also leads to a balanced assignment at each level of the stratifying characteristics. To retain randomness, the probability of making the "best assignment" to minimize imbalance is set to be 90%.

The randomization algorithm will be implemented in REDCap using published code that operates within "R" statistical software. An interface between REDCap and R software will be created by the project statisticians as a "Shiny app" within the RStudio development environment. The resulting R Shiny app will allow the project's recruitment staff to enter the predictive characteristics for a new participant, will compare the new participant's mix of characteristics to those of current participants, and will produce a "blinded" study group assignment for the new participant. The blinded group assignment will be presented to the recruitment staff as one of four letters: A, B, C, or D. That letter will then be entered into REDCap as the new participant's record is set-up. REDCap will be programmed to link each of the four letters to a study group (two letters for the BSM group and two others for the control group). Only the project statisticians, the project manager and the graduate assistant will know the correspondence between letters and group assignments. Four letters (and a corresponding study "arm" for each one) will be used to make it more difficult for recruitment staff to decipher which letters link to specific study groups and, therefore, to foster the likelihood that blinding to group assignment will be maintained throughout the project.

Justification of Sample Size:
The sample size objective for the study is to recruit N = 280 women who will be randomly assigned to the *BSM* or attention control study groups at a 1:1 ratio (140 per group). This objective provides 80% power (α =0.05, two-sided) to detect a standardized mean difference (Cohen's d) of 0.39 or more between the *BSM* and attention control groups. It also provides 80% power to detect an odds ratio of 2.5 or more in exclusive BF between the two groups, assuming that the exclusive BF rate of the control group will be 10% higher than the national population rate in 2017 at 6, 9, 12, 18, and 24 weeks.[4] These calculations account for "loss to follow-up" as high as 25% at 24 weeks, despite the substantially lower attrition (6%) in our pilot study. Based on our pilot study, we approached 78 women to meet our sample size of 60, with a failed screening rate of 25%. Thus, we intend to approach 374 women, which is 25% higher than our proposed study sample to meet our sample size.[21] We anticipate that approximately 70% of the study sample will be WAHS or HHC patients.

In the pilot study, RM-ANCOVAs (with the baseline value of a measure as the covariate) revealed standardized mean differences larger than d = 0.39 for the "main effect" of the intervention on BNP intensity (d = 0.45), pain severity (d = 0.60), cumulative pain (d = 0.64), and BF self-efficacy (d = 0.48) across the 1-, 2-, and 6-week time points.[22,147] For BNP interference, the value of d was 0.39 at week 1, but smaller at weeks 2 and 6.[22] Furthermore, the odds of exclusive BF in the intervention group are 2.9 times higher than the control group at 6 weeks, which is also higher than the hypothesized OR = 2.5. Therefore, we are confident that the sample size goal will be sufficiently powered to detect intervention effects on key variables for SA1 and SA2. Finally, the sample size estimate does not reflect our plans to conduct analyses based on repeated measurement of outcome variables at the 1, 2, 3, 6, 9-, 12-, 18-, and 24-week time points (due to the dearth of information regarding 24-week outcomes). Generally, the inclusion of data for an outcome variable across additional time points marginally enhances statistical power, especially for testing "main" and "interaction" effects of intervention and time.[167]

Enrollment of Employees:
Employees or Hartford Hospital Employees may be recruited if they receive clinical care from Women's Ambulatory Center, or private obstetric care at Hartford Hospital or UConn Health Center. We will not recruit any women who report to key personnel.

Enrollment of Key Personnel, Spouses or Dependents/Relatives:
We will not recruit key personnel, spouses of key personnel, or dependents/relatives of any key personnel.

For EACH Participant Population Describe Screening Procedures, if applicable

The proposed RCT will be conducted to test the effect of the *BSM* intervention vs. an attention control group on BNP, BF exclusivity and duration, BF self-efficacy and maternal well-being to 24 weeks (Figure 4). Participants at baseline will complete assessments, quantitative sensory testing, and provide buccal cell and/or blood samples for assessment of select pain sensitivity SNPs and DNA methylation and again at 6 and 24 weeks at our research sites. At 1, 2, 3-, 9-, 12-, and 18-weeks participants will complete assessments via smartphone text and the UConn Health Research Electronic Data Capture (UConn REDCap) links, https://health.uconn.edu/clinical-researchcenter/ when women shelter at home. If a participant does not have a smartphone, the study will provide a smartphone for them to receive texts and text links. All participants will receive educational material regarding infant development and age-appropriate play at 4, 8, 12, 16, 20, and 24 weeks to maintain contact and sustain engagement in the study.[168] Following UConn Institutional Review Board approval, all recruitment and initial data collection will occur in collaboration with our clinical partners, at the UConn Health Center, a 234-bed tertiary care academic hospital delivering 700 infants a year with 560 women initiating BF; the Women Ambulatory Services at Hartford Hospital (HH), delivering 1000 infants a year with 800 women of diversity initiating BF (see letters of support) and women receiving private obstetric care at Hartford Hospital, delivering 2900 infants a year with 2320 initiating BF.
Prior to launch of the study, all research personnel will receive training on human subjects' research, HIPAA, and biological safety, handling and transportation. The study designated graduate assistants will develop a study binder of all protocols and each role will be established so that appropriate blinding procedures can be maintained throughout the study duration. Dr. Lucas and the project manager will train all research personnel (graduate assistants, research assistants, and peer counselors) on the standardized intervention, scripts, protocols for women who need referrals or follow-ups for BF support or maternal well-being, documentation of schedule data collection visits, and establish weekly research team meetings.

Anticipated Study Time Frame:
Recruitment will begin in October 2021 and continue through December 2024.

Research activity/Quarter	Year 1				Year 2				Year 3				Year 4			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Start-up, team, training, IRB approval	X	X														
Subject enrollment in Y1=50, Y2=110, Y3=110, Y4=10; Data collection; Data quality management		X	X	X	X	X	X	X	X	X	X	X	X			
Complete follow-up			X	X	X	X	X	X	X	X	X	X	X	X	X	
Presentation at conferences				X				X		X					X	X
Submission of protocol and interim analysis article					X				X				X			
Complete database; Final analyses; Grant preparation, Final report					X		X				X	X	X	X	X	X

Design, Procedures, Materials and Methods:

The proposed RCT will be conducted to test the effect of the *BSM* intervention vs. an attention control group on BNP, BF exclusivity and duration, BF self-efficacy and maternal well-being to 24 weeks

(Figure 4). Participants at baseline will complete assessments, quantitative sensory testing, and provide buccal cell and/or blood samples for assessment of select pain sensitivity SNPs and DNA methylation and again at 6 and 24 weeks at our research sites. At 1, 2, 3-, 9-, 12-, and 18-weeks participants will complete assessments via smartphone text and the UConn Health Research Electronic Data Capture (UConn Health REDCap) links, https://health.uconn.edu/clinical-researchcenter/ when women shelter at home. If a participant does not have a smartphone, the study will provide a smartphone for them to receive texts and text links. The consent will inform the participant that if the phone is lost before the participant withdraws or attends the 6-month research visit, $75 will be deducted from the remuneration for their 6-month visit. All participants will receive educational material regarding infant development and age-appropriate play at 4, 8, 12, 16, 20, and 24 weeks to maintain contact and sustain engagement in the study.[168] Following UConn Institutional Review Board approval, all recruitment and initial data collection will occur in collaboration with our clinical partners, at the UConn Health Center, a 234-bed tertiary care academic hospital delivering 700 infants a year with 560 women initiating BF; and the Women Ambulatory Services at Hartford Hospital (HH), delivering 1,000 infants a year with 800 women of diversity initiating BF (see letters of support) women receiving private obstetric care at Hartford Hospital, delivering 2900 infants a year with 2320 initiating BF.

Prior to launch of the study, all research personnel will receive training on human subjects' research, HIPAA, and biological safety, handling and transportation. The study designated graduate assistants will develop a study binder of all protocols and each role will be established so that appropriate blinding procedures can be maintained throughout the study duration. Dr. Lucas and the study Project Manager will train all research personnel (graduate assistants and peer counselors) on the standardized intervention, scripts, protocols for women who need referrals or follow-ups for BF support or maternal well-being, documentation of schedule data collection visits and establish weekly research team meetings. Dr. Lucas and the Project Manager will conduct internal audits every three months to ensure fidelity in recruitment and procedures.

Table 1: Timeline of procedures

Week	**Day**	**Measure**	**Location**	**Time**	**Compensation**
Prenatal visit	Recruitment	Study flyer, Breastfeeding Basic Information	HH, WAHS, UCHC prenatal clinic	5 min	$0
0	Recruitment	Initial Screen	Hospital/ Smart phone	5 mins	
0	Baseline Assessment	Consent • Verification of CLC evaluation of breastfeeding • Buccal cell swabs and/or blood collection (15 ml or 3 teaspoons) • QST **Questionnaires** • Demographics • Breastfeeding Specific Factors: Maternal and Infant Breastfeeding History	Hospital	1 hr Links will be shared for individua ls to	$25 UConn Greenphire Gift Card or ecard

		• Breastfeeding Log (BL)
		  ○ MAIBB-R
		  ○ Algorithm
		• Breastfeeding Battery (BB)
		  ○ BSES-SF
		  ○ Ongoing Breastfeeding Assessment
		• Pain Interpretation Scales (PIS)
		  ○ Coping Strategies Questionnaire
		  ○ McGill Pain Questionnaire
		  ○ Brief Pain Inventory
		  ○ Visual analogue scale
		• Maternal Well-Being (MWB)
		  ○ NINR CDEs (Anxiety, Sleep, Fatigue, Perceived Stress Scale, Index of Self-Regulation, Self-Efficacy for Managing Chronic Illnesses Scale, Global Health)
		  ○ EPDS
		  ○ Karitane Parenting Confidence Scale
				complete on their own	

1	Days 1-5	**Intervention Group ONLY:** BL: 1 entry/ day Texts 2 times/ week breastfeeding coaching with links to Breastfeeding Modules 1-3 Maternal/Infant Care Modules 1-2	Personal computer/ smartphone	5 mins per entry 10 mins/ module	
	Days 1-5	**Control Group ONLY:** Texts 2 times/ week with links to Maternal/Infant Care Modules 1-2	Personal computer/ smartphone	10 mins/ module	
	Day 5	**Both Groups:** BB, PIS, MWB **Control Group only**: BL	Personal computer/ smartphone	10 mins	$25 UConn Greenphire Gift Card or ecard
2	Days 8-12	**Intervention Group ONLY:** BL: 1 entry/ day Texts 2 times/ week breastfeeding coaching with links to Breastfeeding Modules 4-6 Maternal/Infant Care Modules 3-4	Personal computer/ smartphone	5 mins per entry 10mins/ module	
	Days 8-12	**Control Group ONLY:** Texts 2 times/ week with links to Maternal/Infant Care Modules 3-4	Personal computer/ smartphone	10 mins/ module	
	Day 12	**Both Groups:** BB, PIS, MWB **Control Group only**: BL	Personal computer/ smartphone	10 mins	$25 UConn Greenphire Gift Card or ecard
3	Days 15-19	**Intervention Group ONLY:** BL: 1 entry/ day	Personal computer/	5 mins per entry	

		Texts 2 times/ week breastfeeding coaching with links to Breastfeeding Modules 7-9 Maternal/Infant Care Modules 5-6	smartphone	10mins/ module	
	Days 15-19	**Control Group ONLY:** Texts 2 times/ week with links to Maternal/Infant Care Modules 5-6	Personal computer/ smartphone	10 mins/ module	
	Day 19	**Both Groups:** BB, PIS, MWB **Control Group only**: BL	Personal computer/ smartphone	10 mins	$25 UConn Greenphire Gift Card or ecard
Weeks 4-6	Days 21-40	**Intervention Group ONLY:** BL: 1 entry/ day Texts 2 times/ week breastfeeding coaching with links to Maternal/Infant Care Modules 7-12	Personal computer/ smartphone	5 mins per entry 5 mins/ module	
	Days 21-40	**Control Group ONLY:** Texts 2 times/ week with links to Maternal/Infant Care Modules 7-12	Personal computer/ smartphone	5 mins per entry	
Week 4	Day 26	**Both Groups** Infant development and play modules at 4 weeks	Personal computer/ smartphone	10 mins	
Week 6	Day 40	**Both Groups:** • Buccal cell swabs and/or blood collection (15 ml or 3 teaspoons) • QST • BL • BB, PIS, MWB • Audio taped semi-structured interview: Reflection on participating in the study and the impact on their breastfeeding outcomes	Clinic, smartphone	60 mins 15 mins	$50 UConn Greenphire Gift Card or ecard
Week 8	Day 54	**Both Groups** Infant development and play modules at 8 weeks	Personal computer/ smartphone	10 mins	
Week 9	Day 61	**Both Groups:** BB, PIS, MWB**,** BL	Personal computer/ smartphone	10 mins	$35 UConn Greenphire Gift Card or ecard
Week 12	Day 82	**Both Groups:** BB, PIS, MWB, BL Infant development and play modules at 12 weeks	Personal computer/ smartphone	10 mins	$35 UConn Greenphire Gift Card or ecard
Week 16	Day 110	**Both Groups** Infant development and play modules at 16 weeks	Personal computer/ smartphone	10 mins	
Week 18	Day 122	**Both Groups:** BB, PIS, MWB, BL	Personal computer/ smartphone	10 mins	$35 UConn Greenphire Gift Card or ecard
Week 20	Day 138	**Both Groups** Infant development and play modules	Personal computer/	10 mins	

		at 20 weeks	smartphone		
Week 24	Day 166	**Both Groups:** • Buccal cell swabs and/or blood (15 ml or 3 teaspoons) collection • QST • BL, BB, PIS, MWB • Audio taped semi-structured interview: Reflection on participating in the study and the impact on their breastfeeding outcomes • Infant development and play modules at 24 weeks	Clinic, Interview, smartphone	60 mins 15 mins	$75 + $25 bonus UConn Greenphire Gift Card or ecard

Procedures and Data Collection at each Time Point.
At baseline we will collect demographic information, pain and coping scales, BF measures, maternal well-being symptoms, pain, BF and maternal self-efficacy scales, and quality of life health status.

Subsequently, quantitative sensory testing will be performed on the non-dominant forearm and a buccal cell and/or blood samples will be obtained for analysis of selected pain sensitivity SNPs and DNA methylation. All buccal cell swabs and/or blood (15 ml or 3 teaspoons) samples will be labeled with the participants' identification number. Blood will be kept at room temperature on the clinical unit and during transport, and buccal swabs will be stored in a freezer on the clinical unit at -20 degrees Fahrenheit, until transported to the SON Biobehavioral Lab (BBL) for processing and storage.

Study questionnaires will be administered via electronic surveys using UConn Health REDCap v11 Participant will access the UConn Health REDCap link before discharge to access and view texts, web links, and the video modules on either handheld device (e.g., smartphone, iPad) or computer desktop/laptop. All participants will receive an encrypted text (via UConn Health REDCap with an embedded link from Twilio) or an email per their preference with the study measures via UConn Health REDCap v11 After the initial surveys are completed, participants will be asked to contact a member of the research team to register their Greenphire incentive card. A member of the research team will complete the Greenphire form which includes social security number (field is encrypted), address, email and phone number to initiate the first incentive payment. The PROMPT study does not retain participant's social security number or address in our records. If the participant does not have a social security number, ecards will be provided by UConn School of Nursing business office. The team member will also refer the participant to WAHS and Outpatient Lactation scheduler or the UConn Health scheduler for the 6 week follow up visit.

Intervention Administration. Each group will receive a link to the eight video modules between 3-`5 minutes long that address a different topic. During the first week, the appropriate link to the first video to the BSM intervention and attention control group will be sent. Intervention fidelity will be addressed using Resnick et al's[174] framework of design, training, delivery, receipt, enactment, which will be continuously assessed throughout the study duration. Design fidelity will be applied through a standardized intervention with scheduled interactive texts, text-based daily BF journals and links to modules. Training of the interventionist(s) will be assessed routinely by Dr. Lucas through simulated scenarios and practice sessions using texting and phone scripts. Evidence of treatment will include participants' response to bi-weekly texts and targeted lactation support based on galactogenesis and lactation milestones.[21,27] The research team will monitor intervention fidelity by using the UConn Health

REDCap feature that will allow research team to view the date, time, length, and number of times the participant accesses each module and completes the daily BF journal. Our Project Manager, blinded to initial randomization, will coordinate the research team to send participants texts, follow-up phone calls, and emails as needed, at 1, 2, 3, 9, 12, and 18 weeks to encourage completion of the modules and for BSM intervention, address any BF concerns. After the first week, depending on the participant's preference, encrypted text messages, phone calls and/or emails will be made by the research team to encourage BF data completion.

Data Collection during Follow up. After discharge, both groups will receive an encrypted text via UConn Health REDCap with embedded links from Twilio, a cloud communications platform and a back-up archive feature. The follow-up measures at 1, 2, 3, 9, 12, and 18 weeks (Figure 4) include the participants' weekly BNP, pain coping, BF exclusivity, ongoing BF assessment, BF algorithm and maternal assessment of infant BF behaviors, self-efficacy scales (pain, BF, and maternal), maternal well-being assessments, and perceived well-being scales. Completion of the measures will take about 30 minutes. Our statistician team at weekly meetings will identify any missing data to facilitate contact of participants to complete surveys. At 6 and 24 weeks, participants will complete the above measures and repeat quantitative sensory testing and provide buccal cell and/or blood samples for selecting pain sensitivity SNPs and DNA methylation at our clinical locations. Completion of the measures will take about 60 minutes. At Weeks 4, 18 and 20, participants will receive a prompt in their modules to provide their 6 week and 6-month research appointment day and time. If participants do not provide a date and time, research personnel will reach via text (up to three times) to schedule the appointment.

Blinding. We will employ blinding whenever possible. The PI and all sthe research team members involved in data collection or analysis will be blinded to the randomization of the participants, and some of the research team to the group assignment of participants. The statisticians, project manager and graduate assistant will not be blinded to study assignment and ongoing data collection. Research team personnel will follow a strict script to refrain from discussing participant activities, and by using the data management graduate assistant (unblinded) to coordinate assigned condition activities and data collection and analysis. All participants will be assigned a study number, which will be used to track the study measures and buccal cell and/or blood samples. De-identified data with dummy-codes for assigned condition will be entered into the study database to allow blinded data analysis. Blinding was successfully employed during our pilot study.

Participant Retention. Participants will receive progressive monetary incentives, and to retain trust,[150] the participants in both groups will receive monthly text links to normal infant development and age-appropriate play modules.[150,175]

Measures, survey instruments and questionnaires, (including the collection of demographic data).

Baseline, Process, and Outcome Measurements (Table 2)

All of the BNP measures (visual analogue pain scale and Brief Pain Inventory short form), pain coping (Coping Strategies Questionnaire), BF specific factors including demographics, ongoing BF assessment and algorithm, Breastfeeding Self-Efficacy Scale, maternal assessment of infant BF behaviors, maternal well-being symptoms [PROMIS anxiety, sleep, fatigue, perceived stress], Edinburgh Postnatal Depression Scale, perceived well-being [PROMIS global health],pain sensitivity SNPs, and quantitative sensory testing, were successfully collected in the pilot. The effect of the *BSM* intervention on pain self-efficacy, will be measured by the Self-Efficacy for Managing Chronic Illnesses Scale, the Index of Self-Regulation, and on maternal self-efficacy the Karitane Parenting Confidence Scale and Postpartum Bonding Instrument.

IFSMT Context variables.

Breastfeeding Specific Factors, Physical and Social Environment, Individual and Family Factors and Biomedical Research Informatics Computing System Demographics[169–171] The questionnaires will be used to collect participants' demographics (age, gender, height, weight, race/ethnicity, education, socioeconomic and employment status), BF and medical history (parity, prior BF experience, route of delivery, baseline BNP knowledge, chronic conditions and medication usage), physical and social environment targeting BF support (hospital and home access to professional lactation support, and infant and family characteristics).

Table 2. Individual & Family Self-Management Theory Measures

Pain Sensitivity. Pain and Coping. The Coping Strategies Questionnaire-Revised will assess participants' pain coping strategies (praying, coping self-statement, distancing from the pain, ignoring pain, catastrophizing, and distraction). Participants use a 7-point Likert scale to rate the **frequency** of their use of each coping strategy, *"never do that*" to "*always do that*" and its perceived control over their pain.[172,173] Scores range from 7-42, with higher scores indicating more frequent use of the coping strategy.

Peripheral and Central Pain Sensitivity. Peripheral and central sensitivity will be measured using a standardized quantitative sensory testing battery of *cutaneous mechanical pain sensitivity*, involving measures of threshold, ratings of suprathreshold stimuli, temporal summation and after sensations, and pressure pain thresholds using the participant's non-dominant forearm.[174] The testing battery and equipment will match those used by the gold standard German Neuropathic Pain Network.[137,175] The testing assesses inadequate function (hypoalgesia) as well as gain of function (hyperalgesia) and results are evaluated using age- and gender-matched reference data in pain and control populations.[175,176] Inter-rater reliability of the *quantitative sensory testing protocol* has been reported in several pain clinical trials, with each individual test demonstrating acceptable correlation coefficients.[134,175,177–179]

Candidate pain sensitivity SNPs genotyping. Blood and/or buccal cell samples will be collected at baseline before discharge. Blood will be drawn by trained hospital staff or members of the research team before discharge in the patient's hospital room. At the 6 week and 24 week follow up, blood will be drawn at HH in the lactation room. At the follow up appointments at WAHS, the PROMPT research team member will escort participant to the phlebotomy area. At UCHC, the blood will be drawn at UConn Health BBL or Clinical Research Center. The research team will endeavor to have the blood drawn during routine clinical blood draws. Samples will be transported to the School of Nursing Biobehavioral lab, UConn lab service center or Dr. Young's lab to be processed, and split, volume permitting, for liquid N2 storage of a white-blood-cell pellet for later RNA studies. DNA will be isolated using the Qiagen DNA Easy Kit and QC'd prior to delivery of 500 ng to the lab service centers at the University of Connecticut, such as Center for Genome Innovation (CGI), Microbial Analysis, Resources and Services (MARS) or the School of Nursing Associated Laboratories. Samples will be batched in groups of 10 for processing on The Illumina Methylation EPIC Bead Chip.

Time Points **Module**	Item#	α	T1	T2	T3	T4	T5	T6	T7	T8	T9
Context factors:											
Breastfeeding Specific Factors[20, 21] BRICS Demographics[162-164] Module – FBF	48	N/A	X X	 x							
Pain Coping Strategies[165-166] Module – DB, GI, C, S	27	0.80-0.88	X	X x	X xx	X x	X	X	X	X	X
Quantitative Sensory Testing[167-170]	13	0.94	X				X				X
Process factors:											
Self-efficacy Scale[164,172] Module – DB, GI, C, PN-BF, S,	6	0.91	X	X x	X xxx	X x	X	X	X	X	X
BF Self-Efficacy Scale[173] Module – FBF, BNPS , C, S, CPI	14	0.94	X	X xx	X x	X xx	X	X	X	X	X
Index of Self-Regulation[175,176] Module – BNPS, DB, GI, C, S	9	0.73-0.76	X	X xx	X xx	X x	X	X	X	X	X
Ongoing BF Assessment Survey Module[20,21] – FBF, BNPS , CPI	30	N/A	X	X xx	X	X x	X	X	X	X	X
BF Algorithm[156-158] Module – FBF, BNPS, PN-BF	9	N/A	X	X xx	X x	X	X	X	X	X	X
Maternal Assessment of Infant BF Behaviors[156,157] Module – FBF, BNPS, PN-BF	8	N/A	X	X xx	X x	X	X	X	X	X	X
H&H Lactation Survey[182]	20	(0.75-0.98)		X	X	X	X				
Proximal outcomes: PROMIS Anxiety, Sleep, Fatigue, Perceived Stress Scales[162-164] Module – DB, GI, C, S	6-30	0.79-0.91	X	X x	X xx	X x	X	X	X	X	X
Visual Analogue scale (0-100)[22] Module – BNPS, PN-BF	1	N/A	X	X x	X x	X	X	X	X	X	X
Edinburgh Postnatal Depression Scale[181] Module– C, S	10	0.87	X	X	X x	X x	X	X	X	X	X
McGill Pain Scale[179,180] Module - BNPS, PN-BF	15	0.96	X	X x	X x	X	X	X	X	X	X
Brief Pain Inventory-SF[177,178] Module – BNPS, PN-BF	7	0.77-0.91	X	X x	X x	X	X	X	X	X	X
Distal outcomes: Parenting Confidence Scale[174] Module – FBF, C, S	14	0.81	X	X x	X x	X x	X	X	X	X	X
PROMIS Global Physical Health and Mental Health[162-164] Module – GI, C, S	10	0.81-0.86	X	X	X xx	X x	X	X	X	X	X

T1 = baseline; T2 = 1 week; T3 = 2 weeks; T4 = 3 weeks; T5 = 6 weeks;
T6 = 9 weeks; T7 = 12 weeks; T8 = 18 weeks, T9 = 24 weeks
FBF = Fundamentals of BF; BNP-S = BNP strategies; DB = Deep breathing;
GI = Guided Imagery; PN-BF = Pain neurophysiology related to BF;
C = Catastrophizing; S = Stress reactivity; CPI = Common pumping issues

For buccal cell swabs, participants will be instructed to rinse their mouth with clean water and roll the sterile buccal brush firmly on the inside of both cheeks. The participant will roll one brush for 60 seconds on the first cheek and repeat again on the second cheek. Samples will be transported to the SON biobehavioral lab and stored at -80°C until processing in batches at a UConn lab service center or shipped to Dr. Young's lab for verification of results. Genomic DNA (gDNA) will be isolated from buccal samples using the OMNIgene•ORAL OMR-110). The samples are stable at room temperature for 30 days, allowing transport to the SON biobehavioral lab, UConn lab service center, and/or

shipping to Dr. Young's lab. Genomic DNA SNP genotyping will be completed for six SNPs, *COMT* (4 SNPs; (catechol-o-methyltransferase)), and *OXTR* (2 SNPs) (Table 3) using Taqman SNP genotyping assays (VIC/FAM) and allelic discrimination analysis according to manufacturer's directions using an Applied Biosystems StepOne Plus PCR machine and ABI allelic discrimination software (ThermoFisher Scientific, Waltham, MA). Dr. Young has verified a < 95% call rate for all SNPs included using 10uL samples and manufacturer's running parameters.

Whole Genome Methylation Sequencing. The EZ DNA methylation Gold kit (Zymo Research) will be used for sodium bisulfite conversion of DNA prior to library preparation for DNA methylation of select pain sensitivity SNPs for 40 participants (5 zero and 15 highest pain phenotype per group).[180] All libraries will be prepared using the TruSeq DNA Methylation (Illumina) method with 100 ng of converted gDNA per sample. Bisulfite-converted DNA will be first primed by random hexamers carrying a tag sequence on its 5′ end. Subsequently, the bottom strand DNA will be extended and the 3′ end annealed with another terminal-tagging oligo, which induces the synthesis of the 3′ adaptors. Single-stranded DNA fragments with adaptors ligated will be purified and enriched by traditional PCR according to respective kits' instruction manuals. The resulting PCR products will be cleaned up and quality assessed by an Agilent 2100 Bioanalyzer. Before sequencing, the library will be spiked with other high-complexity sequences, according to the manufacturer's protocol to compensate for the reduced sequence diversity in bisulfite converted libraries. Finally, amplified DNA fragments will be quantified by qPCR or PicoGreen assay and sequenced on NovaSeq 6000 platform to generate 2 × 150 bp paired-end libraries.

SNP	Alleles	Frequency
COMT: **Catechol-O-methyltransferase**		
rs6269	**G>A**	**0.36 (Global)**
rs4633	**C>T**	**0.37 (Global)**
rs4818	**G>C**	**0.30 (Global)**
rs4680	**A>G**	**0.37 (Global)**
OXTR **- oxytocin receptor**		
rs2254298	**G>A**	**0.21 (Global)**
rs53576	**G>A**	**0.31 (Global)**

Table 3. Gene Minor Allele Frequency

IFSMT Process Variables.

Knowledge and Beliefs.

The Self-Efficacy for Managing Chronic Illnesses Scale. The Self-Efficacy Scale[181] is an NINR-recommended common data element adapted to manage BF pain.

Breastfeeding Self-Efficacy Scale - Short Form. The BSES-SF scores > 50 indicating greater maternal BF confidence and demonstrates sensitivity to maternal experience with BF, with BF self-efficacy at 1-week postpartum predicting BF methods at 4 and 8 weeks ($p < 0.001$).[182]

Maternal Self-efficacy. Karitane Parenting Confidence Scale measures maternal self-efficacy with good test-retest discriminant reliability ($r(26) = .88$, $p < 0.0001$), .81 internal consistency, and sensitivity and positive predictive power are 86% and 88%, respectively.[183]

Self-Regulation Skills and Abilities.

Index of Self-Regulation. The Index of Self-Regulation is an NINR common data element used across several populations which assesses an individual's general behavior and change effort to make behavioral changes and modulate thoughts, emotions, and behaviors to achieve goals.[184,185]

Breastfeeding Algorithm. An adaptation of the LATCH scale,[163] through texted UConn Health REDCap link women will assess daily (*BSM* intervention) or weekly (attention control) infant awake/sleep state, signs of hunger, number of attempts to latch, strength of latch and of suck, pattern of pauses and sucks, and time duration of BF sessions.

Maternal Assessment of Infant BF Behaviors. A clinical indicator of four infant BF behaviors based on the nursing personality assessment,[162] maternal report, and digital recording of infant BF behaviors.[156]

Social facilitation.

Ongoing BF Assessment Survey. Maternal self-report of BF experience, adequacy of milk supply, problem-solving BF challenges (BNP), use of pharmacological and non-pharmacological therapies and social support.

IFSMT Proximal Outcomes.

Individual & Family Self-Management Behaviors.

Acute BNP. A visual analogue scale (0 - 100) used to measure BNP intensity during the last BF.[22] Acute BNP will be measured with the short version of the Brief Pain Inventory.[186,187] The Inventory has good reliability and validity with BNP.[186,187] The Inventory has two subscales: pain intensity (4 items) and pain interference (7 items) and collects data on use of analgesics and of non-pharmacological measures.[186] For initial data analysis, the average pain intensity and interference scores will be used, and other measures will be quantified. The McGill Pain Questionnaire short form is a reliable self-report measure of pain perception. It entails 15 verbal descriptors of sensory and affective dimensions of pain and is scored on a 4-point scale (0-none to 3-severe).[188,189] Higher scores indicate higher levels of sensory and affective components of pain (range 0-45). Internal consistency reliability is in the excellent range for total pain score (Cronbach's alpha = 0.96).

Cumulative BNP. A score of acute BNP pain intensity from the VAS (0 - 100) at baseline, 1, 2, 3, 6, 9, 18, and 24 weeks will incrementally (baseline + 1 week, baseline + 1 and 2 weeks, etc.) be added together.

NINR PROMIS Scales for Maternal Well-Being Symptoms. The PROMIS scales of anxiety, perceived stress scale, sleep and fatigue. All PROMIS measures are based on the T-score (mean = 50, standard deviation = 10). In most cases 50 equals the mean in the U.S. general population.[169–171]

Edinburgh Postnatal Depression Scale. Postnatal clinical screening tool for depressive symptoms with any score >10 indicates risk for depression and scores > 13 a depressive illness that requires referral. Women will be referred to their provider for fourth trimester care and may continue in the study. The scale has a sensitivity of 85%, specificity of 77% to identify women at high-risk for depression.[190]

H&H Lactation Survey. A 20-item questionnaire maternal perception of milk supply with a 7-point Likert scale from 1 (strongly disagree) to 7 (strongly agree). Total scores ranged 20 ~ 140, with higher scores representing a higher perceived milk supply. The satiety subscale correlates with insufficient milk supply.[191]

IFSMT Distal Outcomes.

Health Status.

Exclusivity and Duration of BF measured by the Ongoing BF Assessment Survey and the BF algorithm.

Quality of Life.

PROMIS Global Health. Measures overall global physical health (function, pain and fatigue) and mental health (quality of life, satisfaction with social activities, and emotional well-being). (See above for scoring).[169–171]

Kaltura modules

We provide voiced modules as part of our intervention. Please see attachments of breastfeeding intervention, postpartum care attention control, and infant development modules.

Describe opportunities provided to participants to ask questions in order for them to make an informed decision regarding participation.

Participant Recruitment will use active and passive methods successful in our pilot study with the addition of prenatal recruitment in the clinical sites. Passive methods include advertisements via Facebook pages and Instagram targeting women in Connecticut who intend to BF and flyers posted at Hartford Hospital, UConn Health, Connecticut Women, Infants, and Children prenatal clinics, and in the hospital common areas, given to women who express interest in BF during their prenatal care, and included in hospital discharge educational packets. Women who express interest in the prenatal period will be identified by a "sticky note" in Epic to facilitate recruitment in the postpartum period. Active methods include screening the inpatient unit census 3-7 times per week by our clinical partners for women who meet inclusion/exclusion criteria. Women who agree to speak with a member of the research team about the study will be approached in labor and delivery and in the postpartum unit. In order to ask initial screening questions via UConn Health REDCap, an evaluation of the participant's capacity to

consent will be assessed and a HIPAA consent will be obtained. Women will be asked if they have any questions about the study before and screening, and before and after consent. If eligible, women will be consented in a private setting, by a member of the research team trained in obtaining informed consent.[22,95,192] The consent process will be documented at Hartford Hospital and stored with the source documents. Participants will be identified in Epic at both Hartford Hospital and UConn Health to facilitate follow-up at 6 weeks and 6 months.

Evaluation of the study

At 6 weeks, women will be asked in a 10–15-minute audio taped semi-structured interview about their breastfeeding experience. At 6 months, women will be asked in a 10-15-minute audio taped semi-structured interview to review their participation in and the impact of the study (see questionnaire).

Data Analysis and Management

All data will be entered into a password-protected database stored on a firewall-protected server that is maintained by UConn. We will use the existing structure of data management established with our pilot study. The protocols established for trialing and monitoring UConn Health REDCap will be strictly followed. We have designed data collection forms to check for missing data in real-time to avoid incomplete data and routinely monitor data input. Our Project Manager, working with the statisticians, will prepare a weekly data summary, which will be reviewed during weekly team meetings.

Statistical Analysis Overview. Prior to undertaking statistical modeling, descriptive statistics will be determined for the study's key independent and dependent variables in order to evaluate the effectiveness of randomization, to check distributional assumptions (such as normality), to identify potential outlying observations, and to obtain preliminary insights into homogeneity versus heterogeneity of variance for outcome measures. Analyses will be conducted using SAS 9.4[193] and R[194].

SA1. Initially, mixed effects linear modeling will be applied to contrast mean levels of pain at the 1-, 2-, and 3-week time points. The analyses will be repeated for a series of pain outcome measures, including BNP intensity, BNP interference, and cumulative BNP. The models will include "main" effects for intervention and time, an interaction between intervention and time, a random effect for "subject", and the baseline value of the dependent variable as a covariate. Modeling results will be used to test for a time-by-intervention interaction. If the interaction is non-significant, the model will be re-fitted without it and testing will focus on the main effect of intervention. Regression diagnostics will be applied to all models to identify non-normality in residuals and potentially biasing effects of outlying observations. While mixed effects linear models are resistant to the impact of limited amounts of missing data, we will also utilize multiple imputation methods, as described below, to evaluate the sensitivity of model estimates and testing results to missing observations. Following evaluation of intervention effects at the 1-, 2-, and 3-week time points, we will proceed to assess differences in acute and cumulative BNP intensity and interference at 6, 9, 12, 18 and 24 weeks. Additionally, we will investigate whether subject-level "trends" or "growth curves" in pain levels across all eight study time points differ between the intervention and control conditions. If necessary, demographic variables will be included in the regression models both to account for potential confounding effects that might arise via imperfect randomization and to reduce unexplained between-subject variation in outcome variables.

SA2. H2A. We will start by investigating the intervention's effect on proportion of exclusive BF after week 6. Initially, the Pearson Chi-square test will be performed to detect the difference between intervention and control groups at 6, 9, 12, 18, and 24 weeks, respectively. Furthermore, a generalized linear mixed model with a logistic link will be applied to analyze the "main effect" of intervention and time, and "interaction effect" of intervention by time. The procedure to fit and re-fit the model will be similar to the approach for pain measures in SA1. The measure for BF self-efficacy, yield scale scores

which range from 14-70. We will treat BF self-efficacy scores as "continuous" variable and follow the approach in SA1 to investigate the intervention effect on BF self-efficacy over time. **H2B.** Subsequently, we will assess intervention effects on maternal well-being - anxiety, depressive symptoms, fatigue, stress, and sleep disturbance over all the time points. Each of these variables' measurement scores will be treated as "continuous" and effects of the *BSM* intervention will be investigated following a similar approach as for the pain measures in SA1. Because these variables are highly interrelated, we will evaluate their response to intervention effects simultaneously. In this approach, differences in the quadrivariate means of these variables between the *BSM* and attention groups will be analyzed using multivariate mixed effects linear modeling in an approach analogous to that for the pain measures in SA1 but with the inclusion of covariances between random intercepts for the anxiety, depressive symptom, fatigue, and sleep disturbance scores at the subject level. Across the modeling procedures related to SA2, regression diagnostics will be applied to investigate suitability of distributional assumptions and potential biasing effects of outliers.

SA3. We will model effects of pain sensitivity SNPs on quantitative sensory testing measures, BNP intensity and interference, BF outcomes in SA2, and maternal and pain self-efficacy across all the time points. In addition, we will also assess the effects of individual quantitative sensory testing measures on all the outcome measures aforementioned over time. Analyses will utilize "linear/generalized linear" modeling with univariate and multivariate dependent variables, will account for correct temporal ordering among time varying measures, and will evaluate correlations between measures that jointly vary in time in response to other factors/covariates.

We have planned for attrition rates as high as 25%. However, our goal is to minimize attrition by instituting a participant outreach plan –namely, contacting participants to complete modules, providing monthly updates regarding child development, and encouraging women to remain involved. In statistical analyses, we will follow each model based only on "observed data" with sensitivity analyses in which Markov Chain Monte Carlo multiple imputation is used to assess the possibility and impact of "missing at random" data.

Statistical analysis of methylation sequencing data. Post-alignment analysis will be performed by using the MethPipe package (http://smithlabresearch.org/software/methpipe/). First, aligned sequences will be converted to MethPipe format using the to-mr command. Methylation levels and coverage for each symmetric CpG site will be calculated. Average CpG methylation levels of annotated genomic regions, i.e., promoters, exons, repeats, CpG islands/shores/shelves (CGI) will be calculated with the MethPipe roimethstat program. Only high-confidence genomic regions with at least 40 CpG observations from reads in the region will be retained for further analyses. Coordinates of promoters (-1000 bp and +100 bp from the transcription start site (TSS)), exons, introns and intergenic regions will be retrieved from Ensembl Regulatory Build (Ensembl release 101) and CGI annotations obtained from the UCSC Table Browser. Tissue-specific enhancer coordinates (+/- 1000 bp from peak) will be retrieved from the Human Encode Project38 (GRCh38/hg38). Hypermethylated regions and hypomethylated regions will be calculated by the hmr command from the MethPipe package. Unsupervised hierarchical clustering of 2 kb tile methylation will be performed using the R hclust command with the "ward" method. Correlation matrix will be calculated by the R corrplot package. Profile plot will be created by the R seqplots package. Gene ontology analysis will be performed by GREAT and DAVID Bioinformatics Resource 6.8. A Univariate ANOVA, followed by post-hoc Tukey HSD will be carried out to compare methylation within promoter region CGI for the six candidate genes (*OXTR*, *COMT*) identified in the preliminary studies. CGI methylation status of each gene will be assessed individually with control for multiple comparisons between conditions maintained, and post-hoc analysis with Tukey HSD will be adjusted to maintain an overall a = 0.05.

SA4. We will model effects of DNA methylation of *OXTR* and promoter regions of *PRLR* haplotypes for different single nucleotides polymorphisms (SNPs) on BNP and maternal perception of lactation insufficiency, BNP intensity and interference, and BF frequency across all the time points. Tumilara Amoo, will consult with the Institute for Systems Genomics to assist with statistical data analysis and interpretation of EPIC array raw data.

EPIC array raw data will be imported into the statistical analysis software Partek® Genomics Suite® for normalization, quality control, differential analysis and biological interpretations (gene ontology and/or pathway analysis). Statistical calculations (available within the software) will include Logistic Regression, Chi Square, False Discovery Rate, Fisher Exact, Power Analysis, and ANOVA. We propose to use the significance threshold of P<9x10-8 to control the false positive rate for EPIC array DNA methylation studies.

Inclusion/Exclusion Criteria:

Inclusion Criteria

- female
- 18 - 45 years of age
- Patient at HH, WAHS, UConn Health
- given birth < 48 hours to a singleton infant > 37 weeks gestational age
- having intention to BF
- provided standardized BF basics during their antenatal care
- with access to the internet via own smartphone, other device, or study-provided smartphone (provided at baseline and returned at 6-month research visit)
- willing/able to consent to participate
- having ability to read and write English as the intervention has not been tested in Spanish speaking population.
- assessed by a lactation consultant (CLC/IBCLC) during BF before discharge

Exclusion Criteria

- <18 or ≥46 years of age
- women with history of significant mental health disorder (e.g., major depression, schizophrenia, or bipolar disorder) due to additional challenges in the capacity for self-management
- neurological or skin condition that inhibits, diminishes, or otherwise prevents sensation, such as eczema, rash, dermatographism on non-dominant forearm
- delivery of an infant with medical complications or congenital anomalies
- inability to communicate in English – although approximately 23% of the Connecticut population is Hispanic/Latinx (see page 25), women who speak/write in Spanish and other languages beside English will be excluded because our intervention has not been tested in Spanish.

Post Enrollment Exclusion Criteria

Participants who are enrolled in the study may be withdrawn due to any of the following criteria:

- non-compliance with study procedures such as failing to log daily entries and completing data collection points. At each data collection point, participants will be reminded via text to complete the surveys, with pushes from REDCap as needed to encourage completion. If needed, participants are followed up with a phone call or email to complete the surveys. If they do not complete the survey, they will be contacted for the next data point. If they do not complete three consecutive data points, they will be removed from the study, however any data collected will be used in analysis.
- Participants will be removed from the study at their own request.

Potential Harms/Risks and Inconveniences:
There is a potential risk of/for the following (protections or mitigating strategies for each are presented in the next section):

1) Loss of confidentiality and privacy by participating in the study
2) irritation from the cutaneous mechanical and pressure sensitivity using the von Frey monofilaments, tuning fork, and Medoc pressure system. In our pilot study, women did not report adverse pain pressure from the von Frey monofilaments or the Medoc system.
3) Irritation of oral mucosa with collection of buccal cell swab sample. In our pilot study, women did not report any pain or irritation with buccal cell swab sample collection.
4) Irritation, pain, infection, bruising at the site, and fainting associated with venipuncture.
5) Participant burden and inconvenience with the research team contacting the participant with bi-weekly texting, providing educational videos, and weekly assessment measures
6) Eye strain with prolonged period of time looking at the computer/text screen
7) Risks related to BF and infant health outcomes.
8) Risks related to COVID-19 transmission.
9) Risks to the research team against biohazards.

Protection against Risk

1) **Protection against disclosure of participants' privacy**. To minimize the risk of accidental disclosure of participants' private information and to maintain the confidentiality of their data, we will use the data management established during our pilot study and within the School of Nursing P20 Center for Accelerating Precision Pain Self-Management. Participant names will be masked by assigning each a unique participant identifier number (PID#) composed of random numbers (*i.e.,* the *code*). All sources and written data will be stored in a secured, locked PI study-designated office in Mary Marshall Crim's office at Hartford Hospital and Dr. Dana Scott's office at UConn Health. No source or written data will be stored at UConn Storrs School of Nursing. No identifiable information on participants will be retained at other study sites and the key to the *code* will be retained at UConn Storrs. Audio files coded with subject ID, will be uploaded on the day of the interview to UConn Onedrive and then deleted from the audio recorder. UConn Onedrive is HIPPA compliant with 2FA (2 factor authentication). A study team member will open up a Microsoft 365 word document in One Drive. Microsoft 365 word version has a transcription feature under voice. A member of the research staff will upload the .wav file into the word document and select transcribe. The transcribe feature converts speech to a text transcript with each speaker individually separated. A member of the team will listen to the audio file to make corrections on the transcript and edit the transcript. The member of the research team will save the file on One drive for additional analysis. The audio files on Onedrive will be deleted after the transcription has been completed and the study has closed. Only members of the research team has access to the files. The analysis of the transcription will be conducted in a qualitative analysis program, Taguette. Taguette is a web based freeware that will be downloaded onto UConn or HH laptops and computers. Each deidentified transcript will be uploaded into the program. The team will tag sections of each interview that reflect an idea or theme. These coded interview sections will then be collected across interviews to clearly describe an idea. These quotes will be used to answer the questions we are asking. The key to the *code* will be destroyed at the time of study closure with the IRB, and de-identified data and samples will be kept indefinitely. Electronic data will be stored on firewall-protected servers with access via computers that are password-protected and kept in locked buildings. Access to research data will be made available only to the investigators, and on an as needed basis to others on the research team. Information obtained as part of the study will remain confidential and not be disclosed to anyone (besides the participant) who is unaffiliated with UConn without consent from the participant, except as required by law or regulation. No information will be used in subsequent publications that would identify individual subjects.

2) **Protection against risk related to *cutaneous pain testing equipment.*** There is a minimal risk associated with the quantitative sensory testing component of this protocol. Some women may not

tolerate the mechanical pressure of the quantitative sensory testing. The quantitative sensory testing mechanical pressure stimulator's controller is equipped with an emergency shut-down feature, which will be engaged if the stimulator's pressure is more than women can tolerate. The participant will always be free to move away from the stimulus or to stop testing at any time. The device and these types of stimuli have been widely used within our group and in groups around the world for many years with no adverse events.[137,175] In our pilot study, all participants completed the sensory testing. In our pilot we found women how responded to mechanical stimulation was predictive of pain sensitivity. There is minimal risk associated with mechanical sensitivity measurement via punctate probes. The punctate filaments have a blunt tip that allows them to indent the skin without causing a puncture. Further, there is a finite amount of force that can be applied with any one filament. We will assess vibration detection via a tuning fork. This instrument has minimal to no chance of causing injury. The fork will be set to vibrate and the blunt base of the fork will be placed against the skin surface.

3) **Protection against risk related to buccal cell swab samples**. There is minimal risk associated with buccal swab sample collection causing irritation of the mucosa. Women will be instructed to rinse their mouth with clean water to minimize bacterial contamination and decrease risk for irritation and infection from oral flora, before rolling the sterile buccal brush firmly on the inside of the cheek (10 times). The likelihood that these problems will occur is low.

4) **Protection against risk related to venipuncture for blood samples**. There is a minimal risk associated with blood draws which include irritation, pain, infection, bruising at the site, and fainting. Only experienced hospital or research staff will draw blood and no more than 2 attempts will be made to obtain blood.

5) **Protection against risk of symptoms of maternal well-being distress**. All participants will receive a pamphlet for the Hartford Hospital affiliated Institute of Living Peripartum Mood Disorder group, Postpartum Support International and suicide hotlines in their hospital discharge packet. Research team members at baseline will be trained to identify participants who exhibit emotional distress and will contact the PI for further questioning and consideration of referral to a mental health professional or social worker before hospital discharge if necessary. Secondly, the research team will check weekly for the Edinburgh Postnatal Depression Scale scores. A score >10 will trigger a texted script to the participant to ask how they are doing, inform them of their concerning score, ask them if they need a referral or follow up with their health care provider. If the participant is unresponsive to text, the PI will follow up with a phone call and immediate referral, if required. If the participant's response includes thinking about suicide, it will trigger an immediate notification to Dr. Lucas, which includes reporting suicide risk to the health care provider (stated in the consent), assisting participant to immediate assessment at an urgent care or emergency department. In our pilot study, out of the 60 women one participant sought treatment for depressive symptoms. The pilot study found that all the women we contacted responded positively to the text and phone call follow-up and appreciated the support and referral for additional support. Likewise, this protocol surveillance addresses the needs of women during the fourth trimester and aligns with the CDC *Hear Her* campaign.

6) **Potential risk for participant burden and inconvenience**. Based on our pilot study results, women reported the baseline data collection to be burdensome. We addressed this risk by removing several questionnaires to decrease participant burden and recruiting during the prenatal period. We anticipate by recruiting women during the prenatal period, women will be prepared for the time for participation and decrease the time burden. Women in the pilot study, reported that completing the paper BF diary 6 times a day was burdensome. For this project, we are using a text-based daily (one entry) BF diary. Women did not report the weekly measurements via UConn Health REDCap as burdensome and that the bi-weekly texting contact was supportive without burdening them to travel to face-to-face visits and places the mother-infant dyad at risk for illness, such as COVID-19. The initial data collection

appointment will take approximately 45-60 minutes. The daily breastfeeding log will take 5 minutes/1 times a day for the first three weeks and from 15 days to 6 weeks a weekly breastfeeding log for 5 minutes a day. The scheduled data collection at Weeks 1, 2, 3, 9, 12, and 18 will take 30 mins to complete. The scheduled data collection for Weeks 6 and 24 will take 60 minutes. Additionally, participants may find logging daily feeding behaviors and multiple questionnaires an inconvenience. Receiving regular texts about their breast-feeding status may also be inconvenient. However, there is evidence to show that support via email and text during the first few weeks of delivery can be beneficial to breast feeding behaviors.

7) **Potential risk for eye strain with prolonged period of time looking at the computer/text screen.** We will instruct participants to use a low light setting and the use of anti-glare software to reduce the strain. Participants will also receive reminders and daily surveys to complete, which may be inconvenient. The time commitment is explained in detail in the consent and will be verbally explained to each subject prior to signing the informed consent. Additionally, we will limit reminders to texts and text pushes via REDCap related to missing data and scheduling 6 week and 6-month research visits, with follow up phone calls as needed to encourage completion, or phone calls to address emergent clinical concerns to decrease the inconvenience to the participant.

8) **Protection of risks related to BF and infant health outcomes.** Infants who BF or formula feed <6 times a day are at risk for dehydration and inadequate calorie intake. Women in the *BSM* intervention group will record daily number of feedings in their daily BF journal. Women in the attention control group will record the number of feedings per day once a week. A record of <6 feedings over a 24-hour period will trigger a notification email via UConn Health REDCap to the research team. The research nurse will contact the participant, evaluate the situation, and decide on the need for referral to a lactation specialist or their healthcare provider. This will also be done on a case-by-case basis. In our pilot study, no participants were referred for inadequate daily feedings. If the participant indicates they are having any difficulty such as mastitis or extreme pain, they will always be told to contact their PCP. Participants at every step of the research study will be encouraged to contact their provider if they are experiencing severe pain or discomfort such as fever.

9) **Protection of risks related to COVID-19 transmission.** Research team members will practice COVID-19 prevention measures at all points of face-to-face contact which include antenatal clinic, inpatient postpartum unit, follow-up data collection at 6 and 24 weeks at the Ambulatory Women's Health Services clinic, Hartford Hospital Lactation clinic, the School of Nursing BBL at UConn Health or UConn Health Outpatient Obstetrics/Gynecology Clinic. These measures will minimize personal density, allow distances, wear personal protective equipment and follow best practice consistent with CDC guidelines, state guidelines, and applicable University and hospital policies. In addition, the study design delivers standardized and best practice BF and BNP problem-solving skills during an acute period of pain when the rate of BF cessation is the highest via mobile technology and when face-to-face visits are most burdensome and places the mother-infant dyad at risk for illness, such as COVID-19.

10) **Protection of research team against biohazards**. All research teams will complete Biohazard and Transportation of Biohazard training through UConn Environmental Safety Department. Collection, or Hartford Hospital Health Stream, storage and assays of biohazardous samples will be performed in accordance with established safety guidelines and regulatory requirements.

Benefits:

Based on our pilot results, we anticipate that participants in the *BSM* intervention group will have decreased BNP intensity and interference and an increase in BF exclusivity. Women may experience satisfaction that future women may benefit through our enhanced understanding of how self-management strategies may decrease BNP, increase BF exclusivity and identify genetic factors that place women at risk for BNP. However, it is possible that women will not perceive any benefit to study participation. Due to the physical, emotional and financial toll of BF pain and the minimal potential risks of the proposed study, the potential benefits to future patients far outweigh potential risks.

Risk/Benefit Analysis:
BNP is the leading reason 1 million women in the United States cease BF before 6 months, the optimal time for infant and women's health. Although there may be no direct benefit to participating in the study, there are minimal risks to participating. Thus, the risk/benefit analysis is dependent on the knowledge to be gained from the study overall. In light of the high likelihood of identifying characteristics (demographic, psychological and/or genetic) of BF pain that influence self-management process and outcomes, findings will be highly relevant to practice, easily accessible and clinically sustainable allowing for large-scale translation in health care and public health settings. In addition to the focus of the research, it is possible that unexpected and/or unrelated information will be discovered that is not the focus of this study. This information will not be disclosed to the participant or to their insurance company.

Economic Considerations:
There are no costs associated with study participation. Aligned with standard practices for increasing participant retention, we are using a scaled incentive plan. At enrollment, women will be informed they will be paid via a reloadable UConn Greenphire gift card or ecard (if they do not have a social security number) after each data collection point and if they participate at all data points, they will receive a study completion bonus. Participants will receive a $25 at baseline, 1, 2, and 3 weeks, $50 at 6 weeks, $35 at 9, 12, and 18 weeks, and $75 at 24 weeks, and $25 as a completion bonus. They can potentially earn up to $355 if they complete the entire study. This amount was derived from estimating the time dedicated to completing the study protocol at each time point.

Data Management:
Source documents (biological, sensory, and questionnaire data) are created for all subject contact protocols and must be initialed and reviewed by the Project Manager and the research team with oversight by the PI once a week. All data will be entered into a password-protected database stored on a firewall-protected server that is maintained by UConn. We will use the existing structure of data management established with our pilot study. The protocols established for trialing and monitoring UConn Health REDCap will be strictly followed. We have designed data collection forms to check for missing data in real-time to avoid incomplete data and routinely monitor data input. Our Project Manager will assist with downloading and updating the database, which will be reviewed during weekly team meetings.
Audio files coded with subject ID, will be stored on UConn Onedrive. Only members of the research team has access to the files. Analysis and coding of the audio files will be conducted on UConn or HH laptops and computers.

Data Safety Monitoring:
We will have several mechanisms ongoing throughout the study as part of the Data Safety and Monitoring Plan and to monitor the potential occurrence of adverse events (AEs). First, the PI and the study staff (Drs. Lucas and Project Manager) will oversee the day-to-day monitoring of all study activities. All data will be stored in locked cabinets within locked offices in the School of Nursing and password-protected computers. Electronic data will be encrypted for storage and de-identified for all study analyses. Data checks, for congruence and missing values, will occur weekly with double-checking (by two research study staff) to ensure accuracy.

Second, participants will be provided with day and after hours contact information for the PI and the study staff, and they will be instructed to report any, and all concerns related to study participation to the PI and/or the study staff. In addition, the PI will have weekly meetings with study staff to discuss study progress (recruitment, data collection and retention), any AEs that occur, and any issues that may arise during the study. Any adverse event that occurs will be directly reported by the PI to the IRB and

sponsoring agency within 24 hours of occurrence. Communication will occur through direct phone calls and follow-up email.

Data Safety and Monitoring Board
The PI will recruit three experts who are not involved with this research study to serve on an independent review committee. Members of the board will be experts in nutrition and BF, self-management related to pain, and genomic statistical methods. The Data Safety and Monitoring Board will review the study protocol prior to activation and develop a Data Safety and Monitoring Board plan. The Data Safety and Monitoring Board will evaluate the data on an ongoing basis and assure participant safety and study integrity. The Data Safety and Monitoring Board will be responsible for monitoring data and for making recommendations based on the data regarding appropriate protocol and any operational changes. The review committee will meet every 3 months to review progress, preliminary data, and any adverse events. They will meet with the PI and CoIs to make recommendations regarding the progress of the study and will be able to report to the Institutional Review Board of the University of Connecticut. Following review, the Data Safety and Monitoring Board will write a report outlining recommendations. These recommendations will be forwarded to the PI and the Institutional Review Board Chair at the University of Connecticut.

Privacy/Confidentiality Part 1
To minimize the risk of accidental disclosure and maintain confidentiality of participants' confidential information and data, each participant will be assigned a unique participant identifier number (PID#). The PID is composed of random numbers, not names, and will be stored separately from the consent form in a locked research area. All participants will be screened using a SID number. The PID data from participants who failed screening will be used to describe and analyze the sample population. Any paper questionnaires will be kept in a locked file cabinet for 6 years in Mary Marshall-Crim's office at Hartford Hospital and Dr. Dana Scott's at UConn Health office until the study ends and will be destroyed at that time. Identifiable key-codes to the data will be retained at UConn Storrs until the completion of all study procedures including all analysis of samples. This is necessary to allow for efficient co-ordination of subject recruitment, and to contact participants for follow-up visits. Buccal cell and/or blood samples will be labeled with ID numbers and stored in a secured research laboratory until it is processed and retained for batch processing. Buccal samples will be stored in the School of Nursing Biobehavioral Lab and be transported to a UConn lab service center or shipped for batch processing at Dr. Young's Laboratory at University of Kansas Medical Center or a UConn lab service center. Genetic samples will be retained for the duration of the study. De-identified biological samples and de-identified data will be made available to all study staff on the IRB protocol for analysis. The key to the subject IDs will only be made available to Dr. Lucas and Project Manager.

All source and written data will be stored in a secured, locked study-designated office in Mary Marshall-Crim's office at Hartford Hospital and Dr. Dana Scott's office at UConn Health. No source or written data will be stored at UConn School of Nursing. Electronic data will be collected and stored on UConn Health REDCap and firewall-protected servers with access via computers that are password-protected and kept in locked buildings. Access to research data will be made available only to the PI and on an as needed basis to other study staff. Information obtained as part of the study will remain confidential and not be disclosed to anyone unaffiliated with UConn without consent from the participant, except as required by law or regulation. No information will be used in subsequent publications that would identify individual subjects.

Once study analyses of the samples have been complete, all de-identified data will be retained indefinitely**.** Participants will have the option of leaving their contact information to be part of future studies. If they consent to that, we will keep a listing of the contact information in a pool for future studies in a secure encrypted file or in a secure locked cabinet until the remainder of the study.

Informed Consent

Consent/permission Setting:
All eligible individuals will meet with a trained research team member and will be asked to read and sign the study consent form prior to enrollment. The consent form addresses the following issues; 1) the purpose of the study, which is to examine the feasibility of the BSM intervention, 2) each of the measurements that will be made in the study will be discussed, 3) the ability of the participant to obtain and continue to receive medical care will not be affected adversely if they choose not to participate in the study, 4) each participant will be responsible, along with their insurance carrier, for clinical care costs, and 5) if at any time the participant feels that they do not wish to continue to participate in the research study during data collection they can discontinue their participation.

Informed consent will be obtained in a private area at Hartford Hospital or UConn Health Center with a research team member trained in providing informed consent. They will have as much time as needed to make a decision. The research team members will give them a consent form to review and return at a time that is convenient for them if they decide to participate before, they are discharged home. Privacy will be maintained by ensuring a private setting for the consent process. Potential participants (or their accompanying legal guardian) will be asked to read through the consent form and will be given adequate time to read and ask questions. Using the script, the research team number will ask the participants basic questions about the research (purpose, procedures, risks, voluntary nature) and ask if the participants have any questions about the research. If the potential participant is interested in the study, they will be asked to sign the consent form.

Capacity to Consent:

Eligible participants will have full decision-making capacity and ability to read and speak English. The research team will document the capacity to consent for each participant which will be kept with the participant's consent. Exclusion criteria for the study include individuals with known psychiatric diagnosis of bipolar disorder or schizophrenia. Research assistants, graduate assistants, and peer counselors at Hartford Hospital are Latina, Black, and Caucasian, which will facilitate recruiting and collecting data for the 23% of women in Connecticut who are Hispanic and with this collaboration we anticipate planning future studies to target Spanish speakers after the Spanish version of the intervention has been tested.

Waiver or Alteration of Consent:

We are requesting waiver of signed consent for conducting the screening form prior to recruiting participants in the study. The initial screen will collect information about demographics and medical history as well as contact information, which are essential to determine if the participants will fit into the inclusion criteria of the study and allow for more efficient recruitment. The research presents no more than the minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of research context.

The participants will be asked to provide HIPPA consent at the beginning of the preliminary screen that all information they give is voluntary and skip any question they are not comfortable in answering. They will be told that we will take all necessary steps to protect their privacy, but it cannot be 100% guaranteed. The HIPPA consent will be filed with the participant's consent file.

We will take all necessary measures to ensure confidentiality is protected. The risks will be minimized by taking the following measures: The capacity to consent, HIPPA consent and study consent will be stored in locked cabinets in Mary Marshall-Crim's office at Hartford Hospital and Dr. Dana Scott's office at UConn Health. The screening and patient response to surveys will be stored in UConn Health REDCap encrypted platform. The screening will be conducted on a confidential phone line in a private room or in a private setting in the hospital suite. The enrollment log will be stored in an encrypted file on a shared document via UConn Storrs OneDrive.

We are requesting the waiver only for the initial screen process, an informed consent process would take place once the participant consents to participate in the study.

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