Postpartum Family Planning

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Initiation of injectable contraception immediately postpartum among breastfeeding women

Protocol

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Collaborating institutions:

The Ohio State University, College of Public Health

The Ohio State University Wexner Medical Center (OSUWMC) and the Department of Obstetrics and Gynecology Clinical Trials Office (CTO)

Emory University School of Medicine, Department of Obstetrics and Gynecology

Short study title: "Postpartum Family Planning" or "Postpartum FP"

I. Background

Ensuring adequate birth spacing could prevent an estimated 9% of deaths worldwide among children less than 5 years of age.[1] Many women, though, are not protected against repeat pregnancy. An estimated 61% of women in their first year postpartum do not want a repeat pregnancy and yet are not using contraception.[2] The lactational amenorrhea method is effective as temporary contraception for breastfeeding women,[3] but its duration of protection varies substantially,[4] and women often fail to start another method before fertility returns. Furthermore, many women do not adhere to their lactation intentions: in a U.S. study, almost one-third of women who stated an intention to breastfeed either did not start or stopped within 6 weeks of birth.[5]

Intramuscular injectable depot medroxyprogesterone acetate (DMPA) is rapidly becoming the contraceptive of choice in some settings, including regions where high maternal and child mortality make birth spacing particularly critical.[6,7] **Advisable timing of DMPA initiation among breastfeeding mothers, though, is in dispute**.[8,9] Progestin potentially could interfere with lactogenesis, milk quality or supply, overall duration, or infant growth.[10,11] While human studies have not identified substantial effects from this exposure on breastfeeding outcomes, they suffer from low power and various possible biases. Given the theoretical risks, the World Health Organization (WHO) advises against use of progestin-only injectables during the first six weeks post-partum among breastfeeding women.[8] In contrast, in its guidance for the U.S., the Centers for Disease Control and Prevention (CDC) recommends that progestin-only injectables generally can be started immediately postpartum on the grounds that their known advantages, as a whole, outweigh their unknown risks.[9] **This inconsistency in guidance reflects the lack of high-quality data for making evidence-based decisions.**

Balancing theoretical risks of harm against known risks of rapid repeat pregnancy has led to contradictions in clinical guidance and practice. While U.S. guidelines permit immediate postpartum DPMA use among breast-feeding women, the practice often is restricted in clinical settings in the U.S. and globally due to concerns ungrounded in rigorous science.

II. Study Summary

We will conduct a randomized controlled trial (RCT) to evaluate the effects of immediate postpartum initiation of DMPA on breastfeeding and long-term contraceptive use. We will enroll approximately 800 adult women who have delivered a healthy, full-term infant at a participating hospital, who intend to breastfeed for ≥6 months, and who want to use DMPA (Depo-Provera; Pfizer Corp.) We will randomize women to **receive within 48 hours of delivery: 1) DMPA ("intervention" arm), 2) placebo injection ("placebo" arm) or 3) no injection ("open control" arm).** The first two arms will be blinded while the open control arm will be unblinded. Note that postpartum patients at the study site do not receive DMPA before discharge as standard care. At enrollment, women will receive condom counseling and provision and referral for contraception at 12 weeks (intervention and placebo arms) or at 6 weeks postpartum (open control arm). We will collect data on lactogenesis, infant feeding and growth, and contraception use during 12 follow-up months. We conducted a pilot study (N=100) in the target population at OSU, which supports the feasibility of the current trial.

III. Objectives

Objective 1: To determine the effect of immediate postpartum initiation of DMPA on breastfeeding. We hypothesize that administration of DMPA immediately postpartum (i.e., before hospital discharge) will not impair breastfeeding compared to administration beginning at 12 weeks post-delivery. To increase the likelihood of detecting a negative effect if one exists, we will evaluate the primary outcome, timing of lactogenesis stage II[12] (onset of copious milk secretion, usually occurring within 96 hours postpartum), as well as a range of secondary outcomes: breastfeeding duration, perceived need for supplementation, use of supplementation, perceived adequacy of milk production, and infant anthropometric measures, including body composition with whole-body air displacement plethysmography (OSUWMC site only).[13-15] Sensitivity analysis will evaluate 1) excluding women in the open control arm and 2) determining whether the findings differ by race.

Objective 2: To determine the effect of immediate postpartum initiation of DMPA on contraception use. We hypothesize that putative DMPA use (i.e., blinded assignment to intervention or placebo arms) will put women on a better trajectory of contraception use by intervening during a time when they likely are highly motivated to avoid pregnancy. In contrast, women who are assigned to start DMPA after a delay risk losing motivation to initiate use. To test this hypothesis, we will compare prevalence of use of a highly-effective contraceptive method at 12 months post-delivery between women in the intervention and placebo arms versus the open control arm. Secondary outcomes will include DMPA use at 12 months. Sensitivity analyses will evaluate 1) whether the findings differ by race and 2) whether the findings differ after restricting the intervention and placebo arms to the subset of women who believe that they were in the intervention arm.

IV. Literature

A. Literature in Support of Objective 1: The relationship between immediate postpartum initiation of DMPA and lactation.

Because delayed lactogenesis stage II is associated with a range of poor breastfeeding outcomes (failure to initiate, reduced duration, and use of supplements),[16-18] identifying any negative effect of progestin on lactogenesis would be important. In theory, progestin could inhibit the process.[19,20] Production of progesterone by the adrenal glands, ovaries and placenta increases during pregnancy. Plasma progesterone levels do not decrease until after delivery of the placenta, after which time, levels decline rapidly, reaching follicular phase levels after 2-3 days. This decline, along with decreased estrogen levels and infant suckling, is thought to trigger lactogenesis. Cases of placental retention, in which lactogenesis has been delayed up to three weeks,[21] support this physiologic mechanism. Also, exogenous progesterone given around the expected parturition time in rats or after fetus removal in ewes inhibits milk secretion; in contrast, no inhibitory effect occurred in rat models when progesterone was given after the establishment of lactation.[19,22,23] Note, though, that progesterone and the synthetic progestogen, medroxyprogesterone acetate, used in the contraceptive injectable are different compounds, which are known to produce different effects in women; thus, **findings from trials on progesterone use in animals are suggestive but cannot be assumed to represent the effects of DMPA use in women.**

A recent systematic review found no RCTs in humans on the effect of immediate postpartum initiation of DMPA on lactation.[10] Three RCTs compared immediate postpartum use of a progestin-only method other than DMPA with the initiation of the same or a different hormonal method later during the puerperium. The three trials made the following comparisons: etonogestrel implant used immediately postpartum versus DMPA at 6 weeks postpartum;[24]

levonorgestrel IUD placed postplacentally versus at 6-8 weeks postpartum,[25] and etonogestrel implant placed at 1-3 days versus at 4-8 weeks postpartum.[26] Three additional RCTs compared initiation of a progestin-only method within 48 hours postpartum – norethisterone enanthate injectable,[27] etonogestrel implant,[28] or daily oral administration of 0.350 mg of norethindrone -- versus placebo.[29] The trial of the levonorgestrel IUD did not find differences between study arms in breastfeeding initiation or continuation at 6-8 weeks but did find that the postplacental arm had less breastfeeding continuation at 6 months.[25] The remaining five trials found no differences in lactation outcomes between groups.[24,26-29] Overall, the six trials were small (20-166 participants) and had short follow-up intervals (2-26 weeks). **Consequently, evidence from the trials is insufficient for ruling out an inhibitory effect from progestin. Furthermore, the trials are non-informative regarding the effect of immediate initiation of DMPA specifically,** as this involves a different type of progestin given through a different route of administration, and involving a larger loading dose of progestin.

Non-randomized evidence regarding the effect of immediate postpartum DMPA exposure on lactation outcomes is inconclusive. Ten observational studies compared breastfeeding outcomes between women choosing to use DMPA starting within the first 6 weeks postpartum compared to women using another or no method.[10] In six of these studies, the upper window for starting DMPA ranged from five days to four months postpartum.[30-35] None of these studies found impaired lactation outcomes (and three found DMPA to be associated with increased breastfeeding duration).[33-35] However, because women in the six studies received DMPA after the typical window for lactogenesis stage II, their findings do not shed light on the potential effects of DMPA initiated before hospital discharge. The remaining four observational studies evaluated the effects of earlier DMPA administration, specifically 1-2 days postpartum,[36] within 72 hours postpartum,[37] or at the time of[38] or before hospital discharge.[5] These study findings were mixed in that early DMPA administration was associated with longer mean breastfeeding duration;[36] with less breastfeeding continuation at four weeks[7] or at three months;[37] or with no difference in duration.[38] Furthermore, these non-randomized studies do not support firm conclusions because 1) they did not control for potential confounders related to women choosing to start DMPA use, which could have introduced substantial bias, and 2) they did not employ standardized, validated outcomes.

No study on DMPA use during breastfeeding has assessed infant adiposity, specifically, as part of a more comprehensive assessment of growth. Increased infant weight gain typically has been interpreted in the breastfeeding and DMPA literature as a positive outcome. However, early hormone exposure theoretically could promote adiposity at the expense of other growth, such as brain and lean mass.[39] Also, excessively rapid infant weight gain, in general, is associated with lifetime cardiovascular risk and is an early indicator of obesity risk.[40] Five cohort studies measured the effect of postpartum DMPA exposure on infant weight gain. The first study (N=331) comparing initiation of DMPA or norethisterone enanthate at either 7 or 42 days postpartum to a non-hormonal comparison arm found no difference between groups in infant weight gain in first three months.[32] However, during months 4-6, infants in the two injectable arms had higher weight gain than those in the comparison arm. The four other non-randomized trials that evaluated infant growth found no difference in weight gain among breastfeeding infants of mothers using DMPA compared to infants in a comparison arm not using DMPA over six months,[31] a mean of 18 months[41] or 4.5 years,[34] or a maximum of 17 years of postpartum follow up.[42] Again, in these non-randomized studies the failure to control for important confounders related to women self-selecting use of DMPA precludes any firm conclusions. Furthermore, despite the assumption in these studies that increased weight gain is a positive outcome, the validity of this interpretation is unknown. By measuring adiposity, we will have a superior measure of the effect of the exposure.

In summary, an inhibitory effect on breastfeeding from immediate postpartum administration of DMPA cannot be ruled out due to the lack of data from RCTs conducted in women, the failure to use validated measures of lactation and the reliance on crude measures of infant growth and adiposity. The data have important limitations: short follow-up intervals, low power, lack of consistency in using sensitive and standardized outcome measures, and the lack of RCTs evaluating DMPA administration specifically in the immediate postpartum period.[43]

B. Literature in Support of Objective 2: The relationship between immediate postpartum initiation of DMPA and contraception use.

Unmet need for contraception remains high among postpartum women. An analysis of Demographic and Health Surveys conducted in 21 low- or middle-income countries found that 61% of postpartum women did not want to become pregnant in the next year but were not using contraception.[2] Likewise, data from the 2006-2010 National Survey of Family Growth found that 35% of pregnancies in the U.S. were conceived within 18 months of a previous birth,[44] putting both the woman and fetus at risk of adverse perinatal outcomes.

Interactions with the healthcare system around the time of childbirth could represent an important window for intervening as women often are highly motivated to initiate contraception use to prevent a closely-spaced, repeat birth. Consequently, the WHO recommends that postpartum women be offered contraceptive counseling and provision following delivery before discharge,[45] and professional bodies in the U.S. (e.g., the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics) advise that prenatal and postpartum care include discussion of contraceptive options and initiation of postpartum contraception.[46] Prenatal and postnatal contraception counseling, though, often are not available or are not offered.[47,48] Contraception counseling is particularly important for women who want to start a new method. Changing method type is common during the postpartum period, with women citing a desire for avoiding repeat births, having improved method reliability, or avoiding safety concerns for the mother or infant.[49]

Interventions delivered immediately postpartum as well as integrating postpartum contraception counseling into immunization and child health services have been shown to increase postpartum contraception use.[47,50] In contrast, recent Cochrane reviews revealed inconsistent evidence on whether providing counseling on postpartum contraception reduces unmet need or repeat pregnancy rates.[51, 52] However, the quality of evidence on effectiveness of the interventions included in the Cochrane reviews was generally low, and the authors argued that more rigorous trials are needed to determine the effects of the timing and elements of postpartum contraception counseling on contraception use and unintended pregnancy rates.

RCTs have shown that a “quick start” of combination hormonal contraception (i.e., starting on the day of the health care visit) can increase contraceptive use compared to the conventional start (i.e., delaying start until the beginning of the next menstrual cycle).[53] The increase in contraception use from the quick start, though, appears to wane over time. However, these findings cannot be assumed to be informative as to the effects of proposed intervention. First, postpartum women could be expected to have different motivation to initiate contraception than a more general population of women. Furthermore, the quick start studies differed from the current trial in that women did not need to return for care to start their method. That is, they either initiated the combination oral contraception or the contraceptive patch immediately or were provided the method to take with them to start later. Finally, these studies did not involve the use of DMPA, which would have required the women assigned to the conventional start to

have returned to the clinic for the method. Postpartum women have substantial new demands on their time that might make it especially difficult for them to return to a facility to obtain contraception during the early postpartum interval.

To date, no RCTs have examined the effect of immediate postpartum provision of DMPA on contraception use. Administering the method at a time when women are highly motivated to avoid repeat pregnancy could help overcome any initial reluctance to start the method and could put women on a better trajectory of contraception use following delivery. While women often discontinue use of methods, including DMPA, a substantial proportion might be motivated to continue to use DMPA. On a population level, this could have huge implications for avoiding adverse consequences of repeat pregnancies. However, no evidence on this is available.

C. Evidence from Preliminary Studies

From September to November 2015, we conducted a pilot study at one of the sites for the current trial, namely, the Labor and Delivery Unit at OSUWMC.[48] We interviewed, before their hospital discharge, 100 postpartum women in the target population (i.e., English-speaking women ≥18 years of age who delivered a term, healthy infant of ≥2500 grams and who intended to breastfeed for ≥6 months). Nineteen percent of survey participants stated that they would "definitely" or "probably" start DMPA before discharge if they were offered the opportunity. The most commonly cited reasons for unwillingness to join the hypothetical trial were the need for more information on DMPA and more time to consider their contraceptive plans. Although professional associations in the U.S. recommend that prenatal visits include contraceptive counseling,[46] almost half (43%) of the participants in this preliminary survey reported not receiving such counseling during prenatal care. Concerns about potential effects of DMPA on lactation did not appear to factor into women's willingness to use DMPA; among those not interested in starting DMPA, only 2% cited concerns about its effects on their breastfeeding infant. Patients also had limited knowledge regarding the methods that are recommended for use during the first six weeks postpartum while breastfeeding. Among women who indicated a willingness to immediately start DMPA, 94% reported being willing to participate in a hypothetical trial that involved completing questionnaires online, and 76% reported being "definitely" or "probably" willing to be randomized to start the method either before discharge or at a later time. Among respondents wanting to start DMPA but indicating a lack of willingness to join the hypothetical study, women cited barriers, such as inconvenient campus parking for returning for follow-up visits.

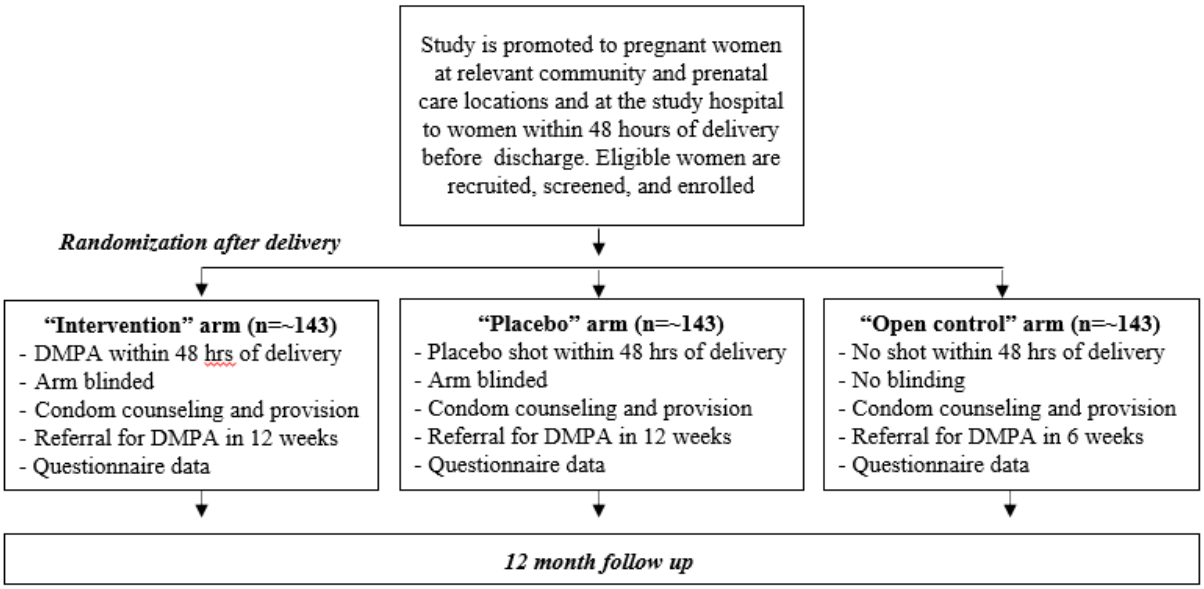
Large numbers of eligible women are available to recruit for the current trial. A review of OSUWMC patient records revealed 3,929 uncomplicated deliveries of term, singleton infants of >2500 grams without any apparent health problems delivered to adult, English-speaking women during 2015. We previously found that 76% of English-speaking, adult women who delivered a singleton, live-born infant at OSUWMC during a five-month interval in 2011 intended to breastfeed their infant.[54] This finding is consistent with a population-based survey in 2014-2015 that found 78% of newborn infants in Ohio initiated breastfeeding.[55] Thus, we estimate an annual expected caseload at the OSUWMC study site of 2,986-3,064 adult, English-speaking women who deliver a term, singleton, healthy infant of ≥2500 grams and who intend to breastfeed their infant. Over the planned 30 months of study enrollment, we would only need to enroll 5.6%-5.7% of eligible women in this group to meet the target sample size. Note that this is well below the 14.4% of breastfeeding women in the pilot study who wanted to immediately start DMPA and were willing to be randomized to the timing of initiation. **Thus, preliminary data support the feasibility of the trial by demonstrating the adequacy of the patient caseload at the enrollment site, OSUWMC.**

V. Procedures

A. Overview

We will conduct an RCT of 429 women and their infant per arm (Figure 1). We will promote the study and enroll eligible, consenting women 1) prenatally at the primary obstetrical facilities that refer to the study sites) for delivery; 2) prenatally at pregnancy-related classes in the community or 3) postpartum at a participating hospital after their delivery and before their discharge. We will enroll approximately 800 women because we anticipate a high number of screening failures before randomization. Our power is based on having approximately 143 women-infant pairs randomized to each of the three arms.

Figure 1. Study design



The study will be partially blinded: participants and study staff, including the study statistician, will be blinded as to the assignment for those in the intervention and placebo arms. In contrast, no one will be blinded as to assignment to the open control arm. (Note that it is not feasible to maintain blinding for the open control arm even among the data analysts given the planned grouping of the arms for the data analyses.) DMPA has a duration of protection of 12 weeks. Women in the intervention or placebo arm will be counseled to refrain from initiating hormonal contraception in the next 6 weeks and to refrain from initiating DMPA in the next 12 weeks. Study staff will use the "Contraceptive choice information sheet" to explain the contraceptive methods that participants can use depending on whether they are assigned to an arm that receives a shot or the arm that does not receive a shot. All participants will be counseled to use condoms post-delivery to avoid a repeat pregnancy (as they either received no shot or could have received a placebo shot). Participants will receive a supply of condoms for either 12 weeks (intervention or placebo arm) or 6 weeks (open control arm), and will be referred to receive DMPA at either 12 weeks (intervention or placebo arm) or 6 weeks post-delivery (open control arm).

Data collection, which will occur at enrollment and through 12 months of follow up, will involve 1) questionnaires on demographics, characteristics and behaviors, lactogenesis, breastfeeding and contraception use and 2) infant anthropometric measures (Table 1).

Table 1. Data collection by objective, location, schedule and mode of collection, and compensation.

Objective	Data collection	Location	Schedule and mode of collection	Compensation
1,2	Enrollment Questionnaire	Participating hospital	Self-administered within 48 hrs of delivery	$80 in cash at OSUWMC; $80 in electronic gift card at Emory-affiliated Hospital
1	Milk Let-Down Questionnaire	Participating Hospital / text, telephone, email	Interviewer administered ≤3 times daily in person at OSUWMC or Emory-affiliated hospital, then daily via text, telephone or email during the first 7 days postpartum until lactogenesis stage II occurs	One payment of $30 in electronic gift card at all sites
1,2	Follow-up Questionnaire	Online	Self-administered at 1, 2, 4, 6, 9 and 12 months. Questionnaires at 1, 6 and 12 months include infant anthropometric measures* from well-child visit data	$10 per interview in electronic gift card at all sites
1	Infant adiposity (PEA POD) and other infant measures*†	OSUWMC only	Measured by trained study staff at 4 months of age	$40 in gift card, a branded gift (e.g., a cell phone popsocket or a pen with light) worth less than $4.00, and either parking pass or transportation by cab to appointment

*OSUWMC = Ohio State University Wexner Medical Center; *Includes weight, length, head circumference; †Visit not completed by participants who delivered at an Emory-affiliated Hospital*

B. Study Population

We will enroll a convenience sample of 800 women. Women can enroll either prenatally or postpartum before their hospital discharge.

To enroll prenatally, women need to meet the following eligibility criteria:

1) Intend to deliver in the Labor and Delivery Unit at a participating ;
2) Are ≥18 years of age;
3) Speak English;
4) Intend to breastfeed, or express milk for their infant, for ≥6 months;
5) Do not want to become pregnant within the first 12 months after delivery;
6) Want to start use of DMPA immediately after delivery before discharge; **AND**

7) Intend to reside in Ohio for those who deliver at OSUWMC or intend to reside in Georgia for who deliver at an Emory-affiliated Hospital for the first 12 months after delivery.

Women will be excluded if they have any contraindications to DMPA (per package insert), which consist of the following:

8) Undiagnosed vaginal bleeding;
9) Known or suspected malignancy of breast;
10) Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease;
11) Liver dysfunction or disease; **OR**
12) Known hypersensitivity to Depo-Provera.

Women who enroll prenatally will need to rescreen following delivery to confirm their eligibility. Women enrolling after delivery or who are rescreening will need to meet criteria 2-12 above as well as the following eligibility criteria:

1) Are a postpartum patient in the Labor and Delivery Unit at OSUWMC or participating Emory-affiliated Hospital; **AND**
2) Have delivered a term, singleton infant of ≥2500 grams without any apparent health concerns.

C. Outcome Measures

The primary outcome is time to lactogenesis stage II measured with participant reports. Chapman and Perez-Escamilla validated the accuracy of maternal perceptions of the timing of lactogenesis stage II, and we will adhere to their questions and methods.[12] Immediately after enrollment, we will record whether women perceived that their milk "has come in" and, if so, we will capture this event to the estimated post-delivery hour. Participants will be re-asked (up to 3 times daily in person during their hospital stay and then daily via their choice of text, telephone, or email after discharge) during the first 7 days postpartum until the event occurs.

Secondary outcomes include 1) length of breastfeeding continuation, which has been negatively associated with both experiencing a delay in lactogenesis stage II and maternal perception of the adequacy of her milk production;[74] 2) perceived need for supplementation (any and timing); and 3) use of supplementation (any and timing). We will use established questions on breastfeeding (any and exclusive feeding) from the National Immunization Survey, which also are used on the Health and Nutrition Examination Survey (NHANES).[75]

Table 2. Location for recruitment, screening and enrollment by prenatal and postpartum status and type of location

Women	Type of location	Location
Prenatal	Prenatal care at primary obstetrical facilities that refer to a participating hospital for delivery	• Hospital obstetrics-gynecology outpatient clinic • Faculty practices • Primary One health centers
	Local classes for pregnant women in the community	• Lactation, birthing and prenatal yoga classes

		• Tour of study hospitals during pregnancy
Postpartum	Through MyChart Hospital	• OSUWMC and participating Emory-affiliated hospitals

Finally, secondary outcomes will include infant measures collected during the follow-up questionnaire (using maternal reports of data from well-child visits) and during the 4-month visit at OSUWMC. Participants enrolled at an Emory-affiliated hospital will not complete a 4-month visit because the site lacks the ADP system. The latter will include the following: 1) percent fat mass (%FM) and fat-free mass (FFM%) measured using the validated, non-invasive whole-body air displacement plethysmography (ADP) system; 2) length with a SECA 416 digital infantometer; 3) head circumference with metric tape; 4) body weight with SECA 727 digital scale; and 5) skinfold with Holtain calipers. We will ensure consistently high-quality measurement by regular monitoring, assessing reliabilities, and refresher training.

D. Detailed Study Procedures

Recruitment. We will advertise the study to women in the community during their pregnancy and to postpartum women following delivery at the study site before their discharge (Table 2). This recruitment will use a motion graphic video, which can be accessed through women's own electronic devices (see http://go.osu.edu/ppfpstudy). Postpartum patients also can choose to watch the video through the MyChart Bedside tablets at OSUWMC or tablets at Emory-affiliated hospitals via a home screen icon for the video. The URL and QR code for the video are included on the study written materials (poster and brochure). The video describes the following to potential participants: 1) the risk of pregnancy following childbirth among women who are sexually active, but not using a modern contraceptive method, even if the woman is breastfeeding and menses has not yet resumed; 2) benefits of using DMPA to adequately space pregnancies for both maternal and infant health; and 3) overview of the trial.

The approved MyChart message (see file "MyChart Message") will be routed monthly to the subset of OSUWMC and Emory patients who are identified in a query through the Information Warehouse that fit the study inclusion criteria by an Honest Broker. Specifically, the message will be sent only to patients of OSUWMC and participating Emory-affiliated hospitals who are 1) a living patient; 2) active MyChart user; 3) attended a patient visit within the past year; 4) currently pregnant; 5) expect to deliver at a participating hospital; and 6) have an estimated delivery date within the next month.

These patients will receive an email notifying them that they have "A new research study to view" in their MyChart message file. Once they login to their secure MyChart they will be able to review the details of the message and express their interest or decline more information. A "yes" response will release their contact information to the researcher in IHIS. If the volunteer clicks "no" or ignores the message, the researcher will not receive any information about the potential volunteer. The list of MRNs (obtained through IW) will go directly to Research IHIS team. The Research IHIS team will use the identified MRNs to send messages via MyChart. Only the Patients who said "Contact Me" (accepted) the medical record will be viewable by study team.

Screening, enrollment and randomization. Study staff will use the "Eligibility Assessment Form" to screen pregnant and postpartum women who are recruited for the study to determine whether they meet the eligibility criteria.

If they have not already watched the recruitment video, eligible women will be given a tablet and headphones and asked to watch the video. They then will be asked to read the "Combined Consent Form" in a private location. Women will indicate their agreement to participate in the study by signing the "Combined Consent Form." Women will be given an unsigned copy of the "Combined Consent Form" to keep for future reference, as it provides contact information for staff responsible for the conduct of the research study in the event of any questions or concerns.

If screening and signing of the "Combined Consent Form" occurs during the prenatal period, the participant will be rescreened – using the same "Eligibility Assessment Form" – after delivery before randomization. In this case, rescreening is to ensure that she meets the eligibility criteria before randomization.

Randomization will occur after delivery (ideally within 48 hours) and before hospital discharge. Stratified randomization with random permuted blocks will be generated using the randomization function within the electronic data capture system, REDCap.[73] This process serves to conceal the allocation process by automatically revealing the arm assignment only upon study enrollment. To minimize the potential for attrition or crossover between arms, participants who are randomized to the intervention or placebo arm will be administered their assigned shot (under blinded conditions) immediately after randomization. Research pharmacy staff will ensure the correct shot is given to the correct participant by checking the randomization documentation before dispensing.

Participants will complete the "Enrollment Questionnaire" on demographics, reproductive history, attitudes and intentions on related topics including breastfeeding.

Participants will be referred for DMPA at 12 weeks if in the intervention or placebo arms and at 6 weeks if in the open control arm. Participants will receive referrals for financial assistance for DMPA as appropriate. Participants will be counseled to use condoms for all sexual intercourse before receiving DMPA and will receive a supply of condoms for 12 weeks (intervention or placebo arms) or 6 weeks (open control arm). Interviewers will administer the short "Milk Let-Down Questionnaire" up to three times daily in person before discharge or until lactogenesis II occurs.

Follow up. If lactogenesis II does not occur before hospital discharge, participants will be asked to complete the "Milk Let-Down Questionnaire" daily via telephone, text or email for the first 7 days postpartum until the event occurs.

Participants will be instructed to complete an online "Follow-up Questionnaire" at 1, 2, 4, 6, 9 and 12 months post-delivery. The "Follow-up Questionnaire" will collect data on breastfeeding behaviors and perceptions; contraception use; and infant physical measurements from well-child visits. If the participant does not have the information from her infant's well-child visit on-hand or if the information that she provides is incomplete or appears to be inaccurate, we will extract the data on the infant's weight, length and head circumference from the medical records at their pediatrician's office.

Participants enrolled at OSUWMC will be asked to return with their infant to OSUWMC for a four-month visit, during which infant measures will be collected (infant adiposity via PEA POD, weight, length, head circumference and skinfold) and recorded on the "Four-month Visit Form." If women have not already completed their 4-month online "Follow-up Questionnaire" at the time

of the in-person visit, they will be instructed to do so using a computer established for this purpose at OSUWMC.

Figure 2. Syringe unmasked (left) and masked (right) with amber tinted tape

Compensation. Participants will receive compensation (amounts specified in Table 1) for their time and travel expenses. The compensation amounts are in-line with recent research with similar populations.

Blinding. Blinding of the investigational product is critical to the integrity of the study. Participants and study staff will be blinded to the study drug assignment to the intervention and placebo arms. The Investigational Drug Services (IDS) Pharmacy at the study sites will have responsibility for organizing the blinding and preparing the injections. The IDS Pharmacy provides support to clinical trials at the study site and operates in compliance with all relevant regulatory and institutional policies. An unblinded pharmacist will prepare the injections in such a way as to ensure the masking of the contents of the syringe. The three study arms will receive the following: 1) intervention arm will receive DMPA injection; 2) placebo arm will receive 0.9% sodium chloride injection; and 3) open control arm will receive no injection. After completion of randomization and treatment allocation, study medication (i.e., DMPA injection or 0.9% sodium chloride injection) will be withdrawn into a 1mL syringe. Syringes will be masked using amber tinted tape to ensure blinding (see Figure 2).

Data collection and management. All study data will be recorded into the PHI version of the electronic data capture system, REDCap.[73] Supported by the OSU Center for Clinical and Translational Science (CCTS), REDCap facilitates the transmittal of secure, encrypted and password-protected data. CCTS will program the data entry screens (with audio component options for participant-administered questionnaires), implementing built-in skip patterns and quality control checks. Data will be instantaneously uploaded behind the secure OSU firewall. The PI will monitor data during the study to resolve potential issues upon detection.

Participants' privacy and the confidentiality of data will be protected through training of interviewers and other study staff; conducting all interviewing, and physical examinations in private; storing study materials in a locked room; and securing computer files that include identifiers. The linkage between the PINs and the participants' identifying information will be maintained in a REDCap form. Otherwise, only the study PINs will identify participant research records. The form with the linkage between the PINs and the participants' identifying information and all other identifying information (e.g., signed consent forms) will be destroyed after the primary trial findings are published. Data identifying individual study participants will not be published or released to persons outside of the project. Non-identifiable study data will be retained for at least five years after study close-out.

Minimizing attrition. We will implement strategies used by the study team in other studies that have achieved high retention of participants during follow up. These targeted efforts will include 1) providing information to participants at each encounter about the importance of attending the scheduled study visits or completing the telephone or online questionnaires, 2) providing

participants with appointment cards, 3) telephoning, emailing or texting participants 1-2 days before their upcoming data collection as a reminder or immediately after any missed follow up; 4) streamlining procedures to allow participants to complete assessments quickly; and 5) keeping data collection instruments as concise as possible to avoid participant fatigue. We will request that participants provide multiple, acceptable methods for contacting them (updated, as needed, at each contact). Women who miss a rescheduled appointment will not be contacted again for the visit in case they have changed their mind about study participation.

E. Statistical Considerations

Analysis of Objective 1. A noninferiority analysis will be used for the primary outcome of time to lactogenesis II. Noninferiority trials are appropriate when the goal is to show that a new treatment (immediate postpartum DMPA initiation) is not clinically worse than an active control (placebo injection, open control); this is in contrast to the standard superiority trial, in which the goal is to show that a new treatment is *better* than the control. Noninferiority will be determined based on the relationship of two-sided 95% confidence intervals (CIs) to pre-specified noninferiority margins. Noninferiority of the intervention arm over the other two arms combined will be accepted if the upper bound of a two-sided 95% CI for the mean difference between groups (intervention – placebo and open control) is less than 6 hours. Although a clinical significant delay in lactogenesis has not been well established, this difference is conservatively sensitive for a noninferiority test given that many common medical interventions (e.g., epidural anesthesia, labor induction, and Cesarean delivery) have been shown to delay lactogenesis stage II by up to 12 hours.[77] Furthermore, the interval of 6 hours is consistent with previous research.[12] Sensitivity analysis will evaluate excluding women in the open control arm (i.e., comparing the intervention arm to the placebo arm).

As a sensitivity analysis, we will repeat these analyses accounting for infant sex as a biological variable, as well as potential confounders including maternal factors that could affect lactogenesis: age, pre-pregnancy body mass index, primiparity, psychosocial stress, diabetes, hypertension, unscheduled Cesarean section, and intention at birth to exclusively.[78-80] We also will evaluate whether the relationship of interest (e.g., immediate postpartum DMPA initiation and time to lactogenesis II) varies by maternal Black race. Finally, although we expect only a negligible amount of missing data for the primary outcome, we will assess the sensitivity of results to missing data by performing multiple imputation analyses under both missing at random and missing not at random assumptions.

For secondary outcomes (breastfeeding duration, perceived adequacy of milk production, etc.), we do not have *a priori* set noninferiority margins, and thus a traditional superiority analysis will be conducted (test for significant differences using t-tests or chi-squared tests as appropriate). We will report two-sided 95% CIs for all outcomes so that post-hoc noninferiority analyses could be conducted (i.e., to evaluate whether the CI covers a specified noninferiority margin).

Analysis of Objective 2. A traditional superiority analysis will be used to compare rates of use of a highly effective method of contraception (defined here as DMPA, implant, IUD, sterilization, pill, patch, or ring) at 12 months post-delivery among women in the intervention or placebo arm versus those in the open control arm. An intent-to-treat analysis will be conducted using a chi-squared test to compare the percentages of women using contraception in each group (intervention + placebo versus open control). As a sensitivity analysis, we will repeat this analysis using logistic regression in order to account for potential confounders such as maternal age, parity, gravidity, socioeconomic status, sexual activity, and prior contraceptive history. We will also repeat analyses restricting those in the intervention or placebo arm to the subset of

women who believe that they received DMPA at enrollment regardless of the accuracy of their belief as an additional sensitivity analysis. Furthermore, we will evaluate whether the relationship between immediate postpartum DMPA initiation and contraception use at 12 months differs by maternal Black race.

Given that the contraception use outcome is measured at 12 months, we anticipate some missing data; however, we have no reason to believe dropout will be differential across arms. Thus, we will assess sensitivity of results to missing data using multiple imputation analyses under both missing at random and missing not at random assumptions. The secondary outcome (DMPA use at 12 months) will be analyzed with similar methods.

Sample size. Sample size was based on providing high (90%) power for the primary outcome of Objective 1 (time to lactogenesis II), while also ensuring appropriate power for Objective 2. We assumed that all groups would have a mean of 65 hours with a common standard deviation of 18 hours, based on a previous study,[26] which was consistent with past research.[19,20] Setting the noninferiority margin at 6 additional hours, **with a type 1 error rate of 0.05 (two-sided 95% CI), we require 143 women randomized to each group to achieve 90% powe**r. As this outcome is measured very soon after randomization, we expect to have it measured on all randomized women. However, we note that even if we have a small amount of missing data for this outcome, we will still have high power. For example, if we have 10% missing data (i.e., time to lactogenesis II measured on 128 women per group), we will still have 87% power. Additionally, this sample size ensures adequate power for our sensitivity analysis comparing intervention to placebo (i.e., excluding women in the open control arm); we will have 80% power for the noninferiority analysis comparing these two groups (under the same assumptions as stated above).

The sample size justified for Objective 1 also will provide high power for Objective 2, which will be assessed using traditional superiority analyses. Based on a recent analysis of data from the National Survey of Family Growth,[81] we assume that the rate of highly effective contraceptive use will be 50% in the open control arm. We conservatively assume a 20% attrition rate at 12 months, thus will have n=114 women in the open control arm and n=228 women in the combined injection arms (DMPA; placebo). With this sample size of randomized women, we will have 81% power to detect a contraceptive use rate of 66% in the intervention/placebo group, corresponding to a relative risk of RR=1.32.

VI. Ethical Considerations

A. Potential Risks

This study poses no more than minimal risk to participants. Participants may experience psychological risks associated with answering questions about sensitive topics or reporting attitudes and behaviors, such as their contraception use.

The study intervention under evaluation (i.e., administration of DMPA for contraception within 48 hours of delivery among women intending to breastfeed their infants) is not contraindicated per the medical eligibility criteria for contraception use issued by the U.S. Centers for Disease Control and Prevention.[9] However, while clinical practices often provide DMPA to breastfeeding women, many settings – including the study site – do not routinely offer DMPA to this group during the immediate postpartum period. Thus, the current trial is warranted to address the gap between U.S. guidelines and routine clinical practice. The trial design is ethical given that the U.S. guidelines permit immediate initiation of DMPA among breastfeeding women. Furthermore,

IRBs have approved the conduct of trials involving randomizing women to start contraception at different times with condoms provided for use in the interim (see our trial approved by the CDC IRB[56] as well as other examples.)[57,58]

We will not perform any genetic testing.

B. Protections Against Risk

Several measures have been implemented to minimize the risks to individuals from trial participation. First, during the consent process, women will be advised that they are free to decline study participation and that they can decline to participate without affecting their care at the facility. Participants also will be informed that if they are uncomfortable at any time, they can decline to answer any questions, participate in any study activity, or discuss any topic. If indicated, participants will be referred for counseling services.

Participants also will be informed of their freedom to terminate the interview or visit at any time without affecting their routine heath care at the facility. All interviews will take place in a private setting by interviewers who have been trained thoroughly on the importance of confidentiality, the procedures to protect a participant's confidentiality, and the penalties associated with breaches of confidentiality.

Participants' personal information will be kept confidential. Access to the roster with identifiers will be limited to authorized study personnel. Participants' privacy and the confidentiality of data will be protected through training of interviewers and other study staff; conducting all interviewing in private; storing study materials in a locked room when not in use; and securing computer files that include identifiers or study data. A unique code will be used to identify the participant's study records. The linkage between the PINs and the participants' identifying information will be maintained in a REDCap form. These linkages will be destroyed after the primary study findings have been published.

C. Potential Benefits of the Research to Human Subjects and Others

The trial provides no direct benefits to the research participants. Participants and others may indirectly benefit in the future if the trial shows no difference in immediate initiation of DMPA compared to initiation at 6 weeks postpartum in terms of the effects on breastfeeding and infant development.

The potential risks involved in trial participation are reasonable in relation to the anticipated benefits.

D. Importance of the Knowledge To Be Gained

The research will provide important information on the effects of immediate postpartum initiation of DMPA among breastfeeding mothers and their infants.

E. Incidents and Incident Reporting

Study staff will record information on any adverse events (AEs) that are classified 1) as possibly, probably, or definitely related to study participation and as unexpected or 2) as serious. Adverse events (AEs) are defined as any untoward health-related reaction, effect,

toxicity, or abnormal laboratory result that a study participant experiences during the course of a study that is new or a worsening of a baseline condition.

An *unexpected* AE is one whose specificity or severity is not listed in the DMPA package insert (i.e., bleeding irregularities, bone mineral density changes, cancer risks, thromboembolic disorders, ocular disorders, ectopic pregnancy, and anaphylaxis). Information on expected AEs will be recorded on study data collection forms, but these events will not be reported to the relevant IRBs and NIH unless the event is also serious or is an unanticipated problem involving risks to subjects or others (UPIRTSO).

An AE is considered *serious* if it is fatal or life-threatening, requires in-patient hospitalization or prolongation of an existing hospitalization, results in a persistent or significant disability or incapacity, is a congenital anomaly or birth defect, jeopardizes the participant or requires intervention to prevent one of the outcomes listed above, or any other event deemed serious by the investigator. Study personnel will report any AE to the PI, who will determine 1) its relatedness to study participation and 2) its seriousness.

All serious adverse events (SAEs) will be reported in an expedited manner to the PI. If it is determined that the SAE is unanticipated and anything other than “not related” (i.e., possibly, probably or definitely related), then the PI, or designee, will notify the IRBs of record and the NIH of the event. Non-serious AEs will be recorded on data collection forms but do not require expedited reporting unless they are classified as UPIRTSO.

UPIRTSO are any events or information that were unexpected and indicate that research procedures caused harm to participants or others or indicate that participants or others are at increased risk of harm. An unanticipated problem may involve any aspect of the research study and could involve anyone including participants, research staff, or others not directly related to the study. AEs that are unexpected and related and protocol violations are specific examples of UPIRTSO. (Not all AEs are UPIRTSO, and not all UPIRTSO are AEs.) Examples of other UPIRTSO include 1) a breach of confidentiality; 2) a change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant; 3) halting of the study by a sponsoring agency; and 4) a participant complaint that indicates unexpected risks or that cannot be resolved by the study team. Any possible UPIRTSO will be recorded on the appropriate log and report form. The PI will decide whether the incident meets the definition of UPIRTSO and, thus, requires prompt reporting to the IRBs and NIH.

All adverse events will be managed according to the standard of care for the clinical practice and the judgment of the on-site clinicians.

F. Data Safety and Monitoring Plan

The Regulatory and Ethics Core of The Center for Clinical and Translational Science (CCTS) at OSU will assemble a Data Safety Monitoring Committee (DSMC) – consisting at minimum of a research ethicist / research subject advocate, biostatistician, and obstetrician-gynecologist – to independently monitor the safety of the study. The DSMC will be chaired by Dr. Michael Para, who is Professor in the Department of Internal Medicine at OSU and the Director of the Regulatory Program at CCTS. The DSMC will convene before study initiation and, during this initial meeting, the DSMC will provide recommendations regarding the protocol application and will develop and approve the DSMC Charter for the trial. After trial initiation, the DSMC will review the accumulated data after an initial subset of participants have been enrolled and after half of the participants have been enrolled. The DSMC

will evaluate participant safety and study conduct and progress and will make recommendations to the sponsor and investigators concerning the trial continuation, modification or termination. No specific stopping guidelines will be presented with the data, and stopping early for safety reasons will be based on the judgment of the DSMC.

VII. Protocol Registration

We will prospectively register the trial at the Protocol Registration System (www.clinicaltrials.gov) before enrolling any subjects.

VIII. Internal Validity

A primary limitation of the trial involves potential issues of generalizability. For example, we are restricting the study to exclude infants who are preterm, low birthweight, or have apparent health complications. Consequently, our findings cannot be extended to infant subgroups arguably most in need of the intervention. Although breastfeeding could be especially important for these subgroups, their inclusion could hinder our ability to detect differences attributable to DMPA exposure. A future study would focus on these special groups. Another potential issue is the linkage, albeit controversial, between DMPA and increased risk of HIV acquisition found in non-randomized trials.[82,83] However, even if the ongoing RCT eventually supports a causal relationship,[84] DMPA is a popular method that can be expected to continue to have an important role in the contraception method mix.

The trial will not answer other research questions that may be of interest. For example, we will not evaluate whether early administration of DMPA affects milk composition. Prior assessments have been unable to interpret the clinical significance of any difference detected in milk composition. For this reason, we are focusing on outcomes with clearer clinical significance. While other breastfeeding outcomes are important to maternal and infant health, we selected the primary outcome, timing of lactogenesis stage II, because it is closely tied to the possible mechanism by which DMPA exposure could impair lactation. Furthermore, this outcome is less susceptible to bias than other possible breastfeeding outcomes. For example, breastfeeding duration could be biased if even a minor proportion of participant attrition occurs during follow up and if this attrition were differential by study arm.

We could experience logistical challenges while fielding the trial. We plan to randomize women within 48 hours of delivery. However, to reflect real-life, clinical circumstances, we will randomize women within 96 hours of delivery, if needed. In this case, we would conduct sensitivity analyses to determine whether the timing of the initial DPMA injection affects the primary outcomes.

We will implement strategies to maximize study retention that has been effective in our previous clinical trials. These include collecting (and routinely confirming) detailed contact information to generate follow-up reminders about study activities and visits; conducting contact tracing of participants who fail to complete on-line questionnaires or the in-person 4-month visit; providing the option of completing the questionnaire via telephone for any participant who prefers this mode for any reason (e.g., lack of internet access); streamlining procedures to allow participants to complete follow-up assessments quickly; designing data collection instruments to be as concise as possible so as to not overburden the participants and thereby increase the risk of response error; and providing payments to compensate for time and travel costs incurred by the participants.

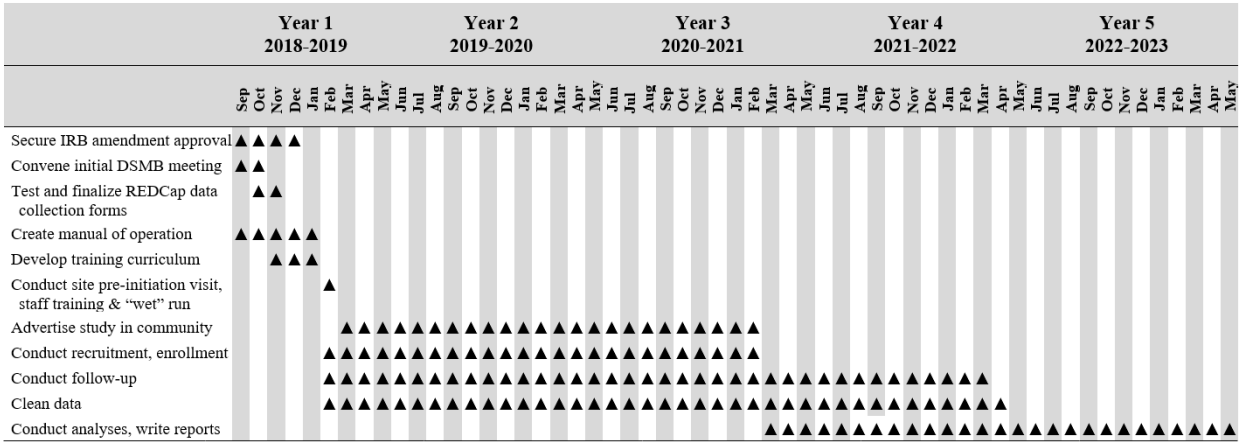
IX. Conclusion

An estimated 135 million women give birth annually[85] and have to decide on contraception to avoid a closely-spaced repeat pregnancy. DMPA is the most popular contraceptive method in some regions, including those in which poor birth spacing contributes to high maternal and infant mortality.[7] However, we lack evidence on the effects of its immediate postpartum use among breastfeeding women. This gap in evidence has led to the WHO and CDC issuing inconsistent recommendations,[8,9] and women having to make a decision regarding initiating contraception postpartum without the information necessary to inform their choice.

We expect the trial findings will permit the harmonization of the WHO and CDC guidance on the timing of DMPA initiation among breastfeeding women.[8,9] The trial findings will be used to directly inform policy and practice in both the U.S. and globally, including in settings where inadequate birth spacing contributes to high maternal and infant mortality.

X. Timeline

Table 3. Project timeline



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The Ohio State University Combined Consent to Participate in Research and HIPAA Research Authorization

Study Title: Postpartum Family Planning

Principal Investigator: Maria F. Gallo, PhD

Sponsor: National Institutes of Health

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your and your child's participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you and your child may leave the study at any time. No matter what decision you make, there will be no penalty to you and your child and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You and your child may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You and your child are being asked to consider participating in this study for the reasons explained below.

1. Why is this study being done?

Using a method of family planning after having a baby helps prevent closely spaced births. Having a repeat birth too soon can be bad for the mother and infant's health.

Depo-Provera is an shot that contains the hormone progestin. The shot is good for preventing pregnancy for 12 weeks. Women can receive the shot right after giving birth.

We are doing this study to better understand the effects of immediate use of Depo-Provera on breastfeeding and long-term use of family planning.

2. How many people will take part in this study?

About 800 adult women and their infant will take part in the study.

3. What will happen if I take part in this study?

We will randomly put women after they give birth into one of three groups: 1) one group will receive the Depo-Provera shot; 2) one group will receive a placebo shot; and 3) one group won't receive any shot. If you are in the Depo-Provera or placebo shot group, you will receive your shot after delivery and before hospital discharge. If you are in the Depo-Provera or placebo shot group, you should not use any hormonal contraceptive method for the next 6 weeks and you should not use Depo-Provera for the next 12 weeks. The placebo shot is made to look the same as the Depo-Provera shot but does not have any active ingredients. The shots are blinded. That means that you won't know whether you receive Depo-Provera or the placebo shot.

Women will be put into the groups by chance, which works like flipping a coin. You and study staff will not be able to choose which group you join. All three groups are very important.

We will ask you questions while you are in the hospital about your health, family planning, and breastfeeding. These questions will take about 20 minutes to answer. We also will ask you repeatedly about your milk let-down while you are in the hospital. During the first days that you return home, we also may ask you these questions again by phone, text or email depending on your choice. These questions will take about 5 minutes to answer.

We will use information from your medical records at OSUWMC and the place where you went to for prenatal care.

We will talk to you about condom use and give you some condoms.

We will ask you to complete a questionnaire either online or by telephone at 1, 2, 4, 6, 9 and 12 months after you give birth. This questionnaire will take about 30 minutes to answer.

We will ask you to return to OSUWMC after four months with your infant so that we can weigh and measure your infant. This visit will take about 30 minutes to complete. We also will use information from your infant's medical records at his or her well-child care visits during the first 12 months.

We may contact you to remind you of the questionnaires or the visit in four months.

If you want to avoid pregnancy during the first year after you give birth, you should get another Depo-Provera shot every 12 weeks or else use another method of family planning. The study will not cover these costs.

4. How long will I be in the study?

Study participation is for the first 12 months after delivery.

5. Can I stop being in the study?

You and your child may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you and your child will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study?

You might feel embarrassed or anxious when you are answering questions. You may choose not to answer any question for any reason.

You may feel slight discomfort from the shot. You may have changes in your menses, such as irregular bleeding, spotting, or no periods.

Studies have found that women lose bone mass density during Depo-Provera use but recover this after they stop using it.

Detectable amounts of drug have been found in the milk of mothers using Depo-Provera. In theory, Depo-Provera could potentially interfere with milk composition, quality, and amount, but no studies have shown that so far. Young infants exposed to medroxyprogesterone (active ingredient in Depo-Provera) from breast milk have been studied for effects on their development and behavior through puberty. No adverse effects have been noted.

7. What benefits can I expect from being in the study?

There are no direct benefits from being in the study. The research could benefit women in general by helping us better understand how to help prevent unintended pregnancy.

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you and your child are otherwise entitled.

9. What are the costs of taking part in this study?

There is no cost to you or your child for being in this study.

10. Will I be paid for taking part in this study?

To pay you for your time, you will receive $80 in cash before leaving the hospital for completing the questionnaire after giving birth.

We will ask you to complete a short questionnaire on milk let-down several times before hospital discharge and then daily at home by telephone, email or text for up to the first seven days postpartum. You will receive a $30 electronic gift card to Walmart or Target once for completing this short questionnaire multiple times.

You will receive a $10 electronic gift card to Walmart or Target for completing each of the six on-line questionnaires during the first year after giving birth (for a total of up to $60).

At the visit in four months, you will receive a $40 gift card to Kroger's for returning with your infant. We also will either give you a parking pass at this time for this visit or provide you with transportation to the visit, depending on which you prefer.

By law, payments to subjects are considered taxable income.

11. What happens if I or my child am injured because we took part in this study?

If you or your child suffer an injury from participating in this study, you should notify the study doctor immediately. This person will determine if you or your child should obtain medical treatment at OSUWMC.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

12. What are my rights if I take part in this study?

If you choose to participate in the study, you and your child may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you and your child may have as participants in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you and your child are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

13. Will my and my child's study-related information be kept confidential?

Efforts will be made to keep you and your child's study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your and your child's records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices; and
- NIH, their agents or study monitors.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search the website at any time.

We will work to make sure that no one sees your survey responses without approval. But, because we are using the Internet, there is a chance that someone could access your online responses without permission. In some cases, this information could be used to identify you.

To help us protect your privacy, the National Institutes of Health has issued a Certificate of Confidentiality for this study. This Certificate will be used to resist attempts to force us to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings.

The Certificate cannot be used to resist a demand for information that is used for auditing or evaluation of federally funded projects or for information that must be disclosed to meet the requirements of the Food and Drug Administration (FDA).

A Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research

information, then we will release the information even though we have the Certificate of Confidentiality.

The Certificate of Confidentiality also does not prevent us from disclosing voluntarily, without your consent, information that would identify you as a participant in the research if required by state and/or federal law. In Ohio, if we have reasonable knowledge that a felony has been or is being committed we are required to notify state officials.

14. HIPAA AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

I. What information may be used and given to others?

- Past and past medical records at OSUWMC for you and your child;
- Medical records for your infant's pediatric visits;
- Research records;
- Information that includes personal identifiers, such as you and your child's names, or a number associated with you as an individual;
- Information gathered for this research about physical exams and questionnaires; and
- Records about any study drug you received.

II. Who may use and give out information about you?

Researchers and study staff.

III. Who might get this information?

- The sponsor of this research: the National Institutes of Health (NIH). "Sponsor" means any persons or companies that are:
  - working for or with the sponsor; or
  - owned by the sponsor.
- Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information;
- If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic or physician's office record;

IV. Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, and other federal and state entities; and
- The Ohio State University units involved in managing and approving the research study including the Office of Research and the Office of Responsible Research Practices.

V. Why will this information be used and/or given to others?

- To do the research;
- To study the results; and
- To make sure that the research was done right.

VI. When will my permission end?

There is no date at which your permission ends. You and your child's information will be used indefinitely. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

VII. May I withdraw or revoke (cancel) my permission?

Yes. Your permission will be good for the time period indicated above unless you change your mind and revoke it in writing. You may withdraw or take away your permission to use and disclose you and your child's health information at any time. You do this by sending written notice to the researchers. If you withdraw your permission, you and your child will not be able to stay in this study. When you withdraw your permission, no new health information identifying you or your child will be gathered after that date. Information that has already been gathered may still be used and given to others.

VIII. What if I decide not to give permission to use and give out my health information?

Then you and your child will not be able to be in this research study and receive research-related treatment. However, if you are being treated as a patient here, you will still be able to receive care.

IX. Is my health information protected after it has been given to others?

There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

X. May I review or copy my information?

Signing this authorization also means that you may not be able to see or copy your study-related information until the study is completed.

15. Who can answer my questions about the study?

For questions, concerns, or complaints about the study, or if you feel you have been harmed as a result of study participation, you may contact **Dr. Maria Gallo at 614-688-2145 or gallo.86@osu.edu**.

For questions related to your privacy rights under HIPAA or related to this research authorization, please contact the **HIPAA Privacy Officer, Suite E2140, 600 Ackerman Road, Columbus, OH 43201**.

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact **Ms. Sandra Meadows in the Office of Responsible Research Practices at 1-800-678-6251.**

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact **Dr. Lisa Keder at keder.1@osu.edu or 614-293-4929.**

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I and my child are being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study and I voluntarily agree for my child to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this combined consent and HIPAA research authorization form**.**

Printed name of adult subject	**Signature of subject** **Date and time** **AM/PM**
Printed name of child subject	**Signature of person authorized to consent for subject (when applicable)**
Relationship to the subject	**Date and time** **AM/PM**

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent** **Date and time** **AM/PM**

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness** **Date and time** **AM/PM**
Printed name of witness	**Signature of witness** **Date and time** **AM/PM**

Emory University and Grady Health System
Consent to be a Research Subject / HIPAA Authorization

Study Title: Postpartum Family Planning

Principal Investigators: Maria F. Gallo, PhD (Ohio State University), Megan Lawley, MD, MPH (Emory University)

Sponsor: National Institutes of Health

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your and your child's participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you and your child may leave the study at any time. No matter what decision you make, there will be no penalty to you and your child and you will not lose any of your usual benefits. Your decision will not affect your future relationship with Emory or Grady Health System. If you are a student or employee at Emory or Grady, your decision will not affect your grades or employment status.
- **You and your child may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You and your child are being asked to consider participating in this study for the reasons explained below.

1. Why is this study being done?

Using a method of family planning after having a baby helps prevent closely spaced births. Having a repeat birth too soon can be bad for the mother and infant's health.

Depo-Provera is a shot that contains the hormone progestin. The shot is good for preventing pregnancy for 12 weeks. Women can receive the shot right after giving birth.

We are doing this study to better understand the effects of immediate use of Depo-Provera on breastfeeding and long-term use of family planning.

2. How many people will take part in this study?

About 800 adult women and their infant will take part in the study.

3. What will happen if I take part in this study?

We will randomly put women after they give birth into one of three groups: 1) one group will receive the Depo-Provera shot; 2) one group will receive a placebo shot; and 3) one group won't receive any shot. If you are in the Depo-Provera or placebo shot group, you will receive your shot after delivery and before hospital discharge. If you are in the Depo-Provera or placebo shot group, you should not use any hormonal contraceptive method for the next 6 weeks and you should not use Depo-Provera for the next 12 weeks.. The placebo shot is made to look the same as the Depo-Provera shot but does not have any active ingredients. The shots are blinded. That means that you won't know whether you receive Depo-Provera or the placebo shot.

Women will be put into the groups by chance, which works like flipping a coin. You and study staff will not be able to choose which group you join. All three groups are very important.

We will ask you questions while you are in the hospital about your health, family planning, and breastfeeding. These questions will take about 20 minutes to answer. We also will ask you repeatedly about your milk let-down while you are in the hospital. During the first days that you return home, we also may ask you these questions again by phone, text or email depending on your choice. These questions will take about 5 minutes to answer.

We will use information from your medical records at Grady, Emory Healthcare and the place where you went to for prenatal care.

We will talk to you about condom use and give you some condoms.

We will ask you to complete a questionnaire either online or by telephone at 1, 2, 4, 6, 9 and 12 months after you give birth. This questionnaire will take about 30 minutes to answer.

We may contact you to remind you of the questionnaires. If you want to avoid pregnancy during the first year after you give birth, you should get another Depo-Provera shot every 12 weeks or else use another method of family planning. The study will not cover these costs.

4. How long will I be in the study?

Study participation is for the first 12 months after delivery.

5. Can I stop being in the study?

You and your child may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you and your child will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with Grady or Emory.

6. What risks, side effects or discomforts can I expect from being in the study?

You might feel embarrassed or anxious when you are answering questions. You may choose not to answer any question for any reason.

You may feel slight discomfort from the shot. You may have changes in your menses, such as irregular bleeding, spotting, or no periods.

Studies have found that women lose bone mass density during Depo-Provera use but recover this after they stop using it.

Detectable amounts of drug have been found in the milk of mothers using Depo-Provera. In theory, Depo-Provera could potentially interfere with milk composition, quality, and amount, but no studies have shown that so far. Young infants exposed to medroxyprogesterone (active ingredient in Depo-Provera) from breast milk have been studied for effects on their development and behavior through puberty. No adverse effects have been noted.

7. What benefits can I expect from being in the study?

There are no direct benefits from being in the study. The research could benefit women in general by helping us better understand how to help prevent unintended pregnancy.

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you and your child are otherwise entitled.

9. What are the costs of taking part in this study?

There will be no costs to you for participating in this study, other than basic expenses like transportation. You will not be charged for any of the research activities. If the study procedures result in any medical complications that would not fall under “injury” as discussed above, the cost of treatment for those complications may be charged to you or your insurance.

10. Will I be paid for taking part in this study?

To pay you for your time, you will receive $80 in electronic gift cards before leaving the hospital for completing the questionnaire after giving birth.

We will ask you to complete a short questionnaire on milk let-down several times before hospital discharge and then daily at home by telephone, email or text for up to the first seven days postpartum. You will receive a $30 electronic gift card to Walmart or Target once for completing this short questionnaire multiple times.

You will receive a $10 electronic gift card to Walmart or Target for completing each of the six on-line questionnaires during the first year after giving birth (for a total of up to $60).

By law, payments to subjects are considered taxable income.

11. What happens if I or my child am injured because we took part in this study?

If you believe you have become ill or injured from this research, you should contact Dr. Lawley at telephone number 404-686-1000. You should also let any health care provider who treats you know that you are in a research study.

If you get ill or injured from being in the study, Emory and Grady Health System will help you to get medical treatment. Neither Emory, Grady Health System nor the sponsor will pay for your medical treatment. Your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurance does not pay, then you will have to pay these costs.

Emory, Grady Health System and the sponsor have not, however, set aside any money to pay you if you are injured as a result of being in this study or to pay for this medical treatment. For Emory and Grady Health System, the only exception is if it is proven that your injury or illness is directly caused by the negligence of an Emory and Grady Health System employee. “Negligence” is the failure to follow a standard duty of care. You do not give up any legal rights you may have by being in this study, including any right to bring a claim for negligence.

12. What are my rights if I take part in this study?

If you choose to participate in the study, you and your child may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you and your child may have as participants in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you and your child are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

13. Will my and my child's study-related information be kept confidential?

Efforts will be made to keep you and your child's study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your and your child's records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- Emory and Grady Health System offices that are part of the Human Research Participant Protection Program and those that are involved in study administration and billing. These include the Emory IRB, the Grady Research Oversight Committee, the Emory Research and Healthcare Compliance Offices, and the Emory Office for Clinical Research; and
- NIH, their agents or study monitors.

Emory and Grady Health System may use and disclose your PHI to get payment for study related treatment and to run normal business operations.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search the website at any time.

We will work to make sure that no one sees your survey responses without approval. But, because we are using the Internet, there is a chance that someone could access your online responses without permission. In some cases, this information could be used to identify you.

There is a Certificate of Confidentiality from the National Institutes of Health for this Study. The Certificate of Confidentiality helps us to keep others from learning that you participated in this study. Emory will rely on the Certificate of Confidentiality to refuse to give out study information that

identifies you. For example, if Emory received a subpoena for study records, it would not give out information that identifies you.

The Certificate of Confidentiality does not stop you or someone else, like a member of your family, from giving out information about your participation in this study. For example, if you let your insurance company know that you are in this study, and you agree to give the insurance company research information, then the investigator cannot use the Certificate to withhold this information. This means you and your family also need to protect your own privacy.

The Certificate does not stop Emory from making the following disclosures about you:

- Giving state public health officials information about certain infectious diseases,
- Giving law officials information about abuse of a child, elderly person or disabled person.
- Giving out information to prevent harm to you or others.

Giving the study sponsor or funders information about the study, including information for an audit or evaluation.

14. MEDICAL RECORD

You already have a Grady Health System or Emory Healthcare medical record. Copies of the consent form/HIPAA authorization that you sign will be put in any Emory and Grady Health System medical record you have now or any time during the study.

Emory and Grady Health System may create study information about you that can help with your care. For example, a note may be added to your medical record to let your doctors know that you are participating in a family planning study. These study results will be put in your Emory and Grady Health System medical record. Anyone who has access to your medical records will be able to have access to all the study information placed there. The confidentiality of the study information in your medical record will be protected by laws like the HIPAA privacy rule. State and federal laws may not protect the research information from disclosure.

Tests and procedures done at non-Emory and Grady Health System places may not become part of your Emory and Grady Health System medical record. Also, if you decide to be in this study, it is up to you to let your other health providers know.

14. HIPAA AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

I. What information may be used and given to others?

- Past and past medical records at Grady Health System and Emory Healthcare for you and your child;
- Medical records for your infant's pediatric visits;
- Research records;
- Information that includes personal identifiers, such as you and your child's names, or a number associated with you as an individual;

- Information gathered for this research about physical exams and questionnaires; and
- Records about any study drug you received.

II. Who may use and give out information about you?

Researchers and study staff.

III. Who might get this information?

- The sponsor of this research: the National Institutes of Health (NIH). "Sponsor" means any persons or companies that are:
  - working for or with the sponsor; or
  - owned by the sponsor.
- Authorized Ohio State University, Emory University, or Grady Health System staff not involved in the study may be aware that you are participating in a research study and have access to your information;
- If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic or physician's office record;

IV. Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, and other federal and state entities; and
- The Ohio State University, Emory University, or Grady Health System units involved in managing and approving the research study including the Office of Research and the Office of Responsible Research Practices.

V. Why will this information be used and/or given to others?

- To do the research;
- To study the results; and
- To make sure that the research was done right.

VI. When will my permission end?

There is no date at which your permission ends. You and your child's information will be used indefinitely. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

VII. May I withdraw or revoke (cancel) my permission?

Yes. Your permission will be good for the time period indicated above unless you change your mind and revoke it in writing. You may withdraw or take away your permission to

use and disclose you and your child's health information at any time. You do this by sending written notice to the researchers. If you withdraw your permission, you and your child will not be able to stay in this study. When you withdraw your permission, no new health information identifying you or your child will be gathered after that date. Information that has already been gathered may still be used and given to others.

VIII. What if I decide not to give permission to use and give out my health information?

Then you and your child will not be able to be in this research study and receive research-related treatment. However, if you are being treated as a patient here, you will still be able to receive care.

IX. Is my health information protected after it has been given to others?

There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

X. May I review or copy my information?

Signing this authorization also means that you may not be able to see or copy your study-related information until the study is completed.

15. Who can answer my questions about the study?

For questions related to your privacy rights under HIPAA or related to this research authorization, please contact the **HIPAA Privacy Officer, Suite E2140, 600 Ackerman Road, Columbus, OH 43201**.

You may contact the Emory University Institutional Review Board at 404-712-0720 or 877-503-9797 or irb@emory.edu:

- if you have questions about your rights as a research participant.
- if you have questions, concerns or complaints about the research.
- You may also let the IRB know about your experience as a research participant through our Research Participant Survey at http://www.surveymonkey.com/s/6ZDMW75.

You may contact Dr. Megan Lawley at 404-778-1384 or ~~Sarah Cordes~~Jamila Jeff at 404-~~778-1358~~828-0663:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research

If you are a patient receiving care from the Grady Health System and have a question about your rights, you may contact the Office of Research Administration at research@gmh.edu.

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I and my child are being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study and I voluntarily agree for my child to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this combined consent and HIPAA research authorization form**.**

Printed name of adult subject	**Signature of subject** **AM/PM** **Date and time**
Printed name of child subject	**Signature of person authorized to consent for subject (when applicable)**
Relationship to the subject	**AM/PM** **Date and time**

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent** **AM/PM** **Date and time**

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness** **AM/PM** **Date and time**
Printed name of witness	**Signature of witness** **AM/PM** **Date and time**