PROTOCOL TITLE:

Open-label randomized control trial and feasibility study of Florjajen Digestion probiotics to reduce GBS colonization in pregnant women by the time of birth.

PRINCIPAL INVESTIGATOR:

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VERSION NUMBER:

4

DATE:

12/2/2021

REGULATORY FRAMEWORK:

Please indicate all that apply:

☐	DOD (Department of Defense)
☐	DOE (Department of Energy)
☐	DOJ (Department of Justice)
☐	ED (Department of Education)
☐	EPA (Environmental Protection Agency)
x	FDA (Food and Drug Administration)
x	HHS (Department of Health and Human Services)
☐	VA
☐	Other:

FUNDING:

Internal, departmental

CLINICAL TRIALS

Is this a clinical trial per the NIH definition of a Clinical Trial? ☒ Yes ☐ No

NIH Definition of a Clinical Trial:

A research study in which one or more human subjects are prospectively assigned to one or more interventions. An "intervention" is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Use the following four questions to determine the difference between a clinical study and a clinical trial:

1) Does the study involve human participants? ☒ Yes ☐ No
2) Are the participants prospectively assigned to an intervention? ☒ Yes ☐ No
3) Is the study designed to evaluate the effect of the intervention on the participants? ☒ Yes ☐ No
4) Is the effect being evaluated a health-related biomedical or behavioral outcome? ☒ Yes ☐ No

Note that if the answers to the 4 questions are yes, your study meets the NIH definition of a clinical trial, even if…

- You are studying healthy participants
- Your study does not have a comparison group (e.g., placebo or control)
- Your study is only designed to assess the pharmacokinetics, safety, and/or maximum tolerated dose of an investigational drug
- Your study is utilizing a behavioral intervention

If yes to all 4 questions, please confirm that the research team is familiar with and agrees to comply with the investigator requirement to register the study on the ClinicalTrials.gov database. Additionally, the approved consent document(s) must be uploaded to the ClinicalTrials.gov database ☒ Yes ☐ No

For any assistance with registration of your trial or the requirements, please contact HSC-CTSCResearchConcierge@salud.unm.edu

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1. Objectives

Our primary research question is "Does taking an oral probiotic agent in healthy, low risk pregnant patients at term reduce the number of *Group B streptococcus* (GBS) positive women at the time of admission to Labor and Delivery (L&D)?" We will be assessing the feasibility of a study of probiotic use in our pregnant, GBS positive population. Our outcome variable is qualitative GBS colonization (positive versus negative). Secondary outcomes include intervention adherence, maternal gastrointestinal (GI) symptoms, and maternal and infant adverse events. We will also collect data on demographics, lifestyle practices (sexual practices, hygiene, and diet), and birth characteristics.

The proposed study is an open-label randomized control trial and feasibility pilot study of Florajen Digestion given to GBS positive women colonization. In this study, we aim to determine whether such a study is acceptable in our population, whether any adverse events are identified, and what barriers or confounding variables might exist to probiotic use at term. We will also look at whether probiotic use had any reported effect on maternal gastrointestinal (GI) symptoms. We hypothesize that women who are GBS positive at 36 weeks gestation and ingest a daily oral prenatal combination probiotic (Florajen Digestion™) until the time of birth will experience a reduction in GBS.

2. Background

The proposed study is an open-label randomized control trial and feasibility pilot study of Florajen Digestion given to GBS positive women. GBS is the most prevalent perinatal infection with profound potential comorbidities for neonates. Vaginal and GI colonization with GBS occurs in up to 30% of adult women. Like most vaginal bacteria, it originates and ascends from intestinal microbes (Bolton et al., 2008). In the typical healthy vaginal environment, the bacteria Lactobacillis predominates while Bifidobacterim predominate in the human GI tract. Both Lactobacilli and Bififobacterium prevent adherence of pathogens such as GBS on mucosal surfaces, thereby reducing GBS colonization (Donders, 1999; Fooks & Gibson, 2002; de Vrese, 2009; Reid Dols, & Miller, 2009; Strus, Malinowska & Heczko 2002).

Colonized pregnant women can pass GBS to their neonates during vaginal birth, putting the neonate at risk for Early Onset *Group B Streptococcus* Disease (EOGBSD), which is associated with a neonatal mortality rate of 5-10%. Prevention of EOGBSD is an ongoing challenge for health professionals involved in perinatal care. The Centers for Disease Control and Prevention (CDC) 2010 guidelines updated by American College of Obstetricians and Gynecologists (ACOG, 2019) require universal antepartum GBS screening and Intrapartum Antibiotic Prophylaxis (IAP) for GBS positive women. While use of these guidelines has significantly reduced the incidence of EOGBSD, up to 30% of laboring women and their fetuses are exposed to IAP. Comorbidities associated with IAP exposure for both the mother (increased incidence of antibiotic resistance, allergic sensitization, diarrhea including *Clostridium difficile,* and fungal infections), and the neonate (*Escherichia coli* infections and greater risk of allergic sensitivity) are significant

problems. In an attempt to avoid the comorbid problems associated with the current use of IAP during labor, the proposed study will test a low cost, safe, innovative approach to reduce prenatal colonization with GBS while adhering to the CDC prevention guidelines. We hypothesize that women who are GBS positive at 36 weeks gestation and ingest a daily oral prenatal combination probiotic (Florajen Digestion™) until the time of birth will experience a reduction in GBS colonization.

Several studies have established the potential for probiotics to reduce GBS colonization. Meta-analyses of women's health applications of probiotics have been published by Abad & Safdar (2009) and this work was extended by Hanson, VandeVusse, Safdar and Abad (2014). A predominance of Lactobacillus in vaginal flora was associated with reduced GBS colonization in several studies. In an observational study, pregnant women with more vaginal Lactobacillus were found to have lower rates of GBS colonization (Moghaddam, 2010). Ronnqvist et al., (2006) conducted a RCT of 191 nonpregnant women and found that a perineal topical probiotic intervention reduced the presence of GBS in vaginal flora. Moghaddam (2010) observed the vaginal flora in 201 pregnant Iranian women who did not receive a probiotic intervention and found that the presence of Lactobacillus was inversely related to GBS colonization. This feature of probiotics has led to six clinical trials of probiotics to reduce antenatal GBS colonization worldwide (Martin et al., 2019; Di Pierro et al., 2016; Ho et al., 2016; Olsen et al, 2018; Hanson et al, 2014; Sharpe et al., 2019).

Five of these trials are reviewed here, and the remaining study by Dr. Hansen et al (2014) will be described later. It should be noted that there were no adverse outcomes in mothers or newborns documented in any of these trials. De Pierro et al (2018) demonstrated the safety of Streptococcus salivarius K12 and reduction in gut disorders. In their open-label cohort, 170 women started probiotics at 30 weeks gestation and were compared to 279 controls. They found a 6% decrease in the GBS colonization. A RCT by Ho et al (2016) included 49 probiotic participants and 50 placebo participants. The intervention group consisted of GBS positive women who started probiotics at 36 weeks gestation. Participants took probiotics an average of 20 days. GBS colonization decreased significantly in the probiotics group (21/49=42.9% significant (Chi Square; p=0.007) vs 9/50-18% placebo). A similar RCT by Olsen (2018) included 21 probiotic participants and 21 placebo participants. They also started GBS positive women on probiotics at 36 weeks gestation. They did not find a difference in GBS status for women who took probiotics versus controls, but also noted that only 16 of the 21 participants completed 21 days of probiotic. They also found an increase in commensal microflora in the probiotic group (P=0.048). Martin et al (2019) studied a prospective cohort of 21 participants who took probiotics and 21 participants who took a placebo. Women found to be GBS positive began probiotics at 26 weeks gestation. At 36-38 weeks, about 30% of women in the probiotic group were GBS negative, and the mean GBS CFU decreased significantly from 5.14 at 26 weeks to 3.80 at 38 weeks. A third RCT by Sharpe et al (2019) studied 57 women who took probiotics compared to 56 participants who took a placebo. Women began probiotics at 25-28 weeks gestation. Results showed that mean compliance rate

was 87%. There was no significant difference in GBS colonization between groups (15.8 vs 21.43%; p.48).

These six studies suggest efficacy of probiotic interventions in reducing antenatal GBS colonization despite significant variation in probiotic interventions. Significant variation in probiotic interventions included the use of different species and strains of probiotics, the use of different dosage (1 billion minimum to 15 billion maximum), differences in initiation and duration of probiotics (20 days to 12 weeks), and adherence rates. A meta-analysis of these six clinical trials (n=709) showed that the use of an antenatal probiotic increased the probability of a negative GBS result by 79% (95% CI=0.34-0.92, p=0.02).

Several other factors have been found to affect vaginal flora including sexual activity (Antonio et al, 2009; Newton et al., 1999), vaginal cleaning such as douching (Cottrell, 2010), and dietary intake of active cultured milk products such as yogurt (VandeVusse et al., 2013; Myhre et al., 2011; Brantsaeter et al., 2011).These factors will be addressed in the proposed study as confounding variables.

Two preliminary studies have successfully been completed that provide a foundation for our proposed study. In vitro testing (Ephraim et al., 2012) demonstrated that the live culture, freeze-dried, probiotic combination Florajen3 inhibited GBS when they are cultured together, independent of lactic acid production. Florajen3 has good adherence to epithelial cells in cell culture and resulted in a significant drop in the pH by 5 logs ($P < 0.05$). (Ephraim et al., 2012). Florajen Digestion will be submitted to the same rigorous laboratory testing methods by the Marquette University research team (see below for information on our collaboration with this team).

In vivo pilot testing of Florajen3 was completed in early 2012 in an open-label, randomized control trial study with ten pregnant women taking the probiotic capsule daily and ten pregnant women serving as controls (Hanson et al., 2014). The sample consisted of 50% African-American, 45% Caucasian, and 5% Hispanic women with an overall dropout rate of 30%. At 35-37 weeks gestation, two women in each group had positive GBS cultures. The women in the probiotic group who were GBS positive averaged 68% adherence, while the eight women who were GBS negative averaged 90% adherence. Of the total 4 women who were GBS positive at 35-37 weeks, the two control group women had higher GBS colony counts (7 x102 to 2.07 x105), than the two women in the probiotic group (2 x102). This finding suggests the probiotic intervention suppressed growth of GBS. One of the bacterial strains contained in Florajen3 (B. lactis) was identified by PCR molecular typing from a rectal swab of one probiotic group participant, indicating adherence to the intervention. The study also explored potential confounding variables including yogurt consumption, antibiotic use, and sexual activity. There was a significant inverse relationship between yogurt ingestion and lower rates of GBS colonization (p=.02). There were trends toward higher rates of GBS colonization for women who reported prenatal antibiotic use and oral sexual activity (Hanson et al., 2014). Women in the probiotic group reported no side effects. Five of the ten women in the probiotic group volunteered anecdotes about the intervention decreasing their constipation; therefore, a tool modified to capture GI symptoms associated with

pregnancy was tested. This pilot study was registered on ClinicalTrials.gov NCT02249325 and has been disseminated by publication (Hanson et al., 2014).

We will be collaborating with Dr. Lisa Hanson from Marquette University who has done extensive research on probiotic use and its effect on GBS. Marquette University is currently conducting a phase 2 double-blind placebo-controlled trial of Florajen3 against GBS under Investigational New Drug (IND) #16549 and with NIH/NICHD funding 1R21HD095320-01; Project Period: 07/20/2018 –06/30/2020. This study is registered on clinicaltrials.gov NCT03696953. Dr. Lisa Hanson is a Marquette University Endowed Professor and senior researcher. She will serve as Marquette University co-investigator for this study. Dr. Hanson was PI for the study team that conducted and published the first clinical trial of probiotics to reduce antenatal colonization in the world She is currently conducting an NIH funded study of probiotics to reduce antenatal GBS colonization under FDA IND. The study protocol and measures are her intellectual property and she has generously collaborated with Katrina Nardini, CNM so that these measures can be used in the UNM study. They will serve as co-principle investigators. Dr. Hanson holds the FDA IND for Florajen Digestion and must be involved in the clinical trial for FDA oversight and required reporting. She also has the relationship with the Florajen Digestion manufacturer, who are suppling Florajen Digestion for the study. Dr. Hanson provided two ipads from her research endowment to facilitate study data collection. She will be involved in the data safety monitoring. She will collaborate on all dissemination efforts.

Florajen3, currently used in Marquette University's clinical trial, is no longer manufactured. Therefore, for our research we will use Florajen Digestion as the intervention. Compared with Florajen3, Florajen Digestion has two additional probiotic species. Florajen Digestion is a probiotic combination product composed of freeze-dried strains of live organisms, including Howaru® Dophilus-*Lactobacillus acidophilus* NCFM™; *Lactobacillus acidophilus* La-14; floraFIT *Bifidobacterium lactis* Bi-07™; *Bifidobacterium animalis* ssp. Lactis HN019, floraFIT *Bifidobacterium longum* Bl-05™ for a total 15 x10^9 CFU per capsule. In vitro testing (Ephraim et al., 2012; Appendix A.2.) demonstrated that the live culture, freeze-dried, probiotic combination Florajen3 inhibited GBS when they are cultured together. In vivo pilot testing of Florajen3 was completed in early 2012 in an open-label, randomized control trial study with 10 pregnant women taking the probiotic capsule daily and 10 serving as controls (Hanson et al., 2014; Appendix A.1.). Findings suggested that the probiotic intervention suppressed growth of GBS. Women in the probiotic group reported no side effects.

IND application for Florajen Digestion was submitted to the FDA in late May 2020 and has been granted (IND # 22834). We have received a commitment letter from the producers of the Florajen Digestion to provide the probiotic product for our research study at no cost.

3. Study Design

This is an open-label randomized control trial and feasibility of a larger RCT in our setting that would examine prenatal probiotic use in Group B Strep (GBS) positive pregnant women at term. We hope to address the question of whether prenatal oral probiotic use, taken by healthy low risk GBS positive women from approximately 37 weeks gestation until the time of birth, will reduce the number of women who test positive for GBS at the time of admission to Labor and Delivery (L&D). In this study we aim to determine whether such a study is acceptable in our population, whether any adverse events are identified, and what barriers or confounding variables might exist to probiotic use at term. We will also look at whether probiotic use had any reported effect on maternal gastrointestinal (GI) symptoms.

4. Inclusion and Exclusion Criteria

Inclusion Criteria

Healthy adult (≥ 18 years of age) pregnant women who are 36 – 37 $^{6/7}$ weeks gestation at enrollment [calculated from the first day of Last Normal Menstrual Period (LNMP) and/or ultrasound (US)]

Group B Streptococcus Positive at 36 weeks gestation with:

- No obstetric complication requiring delivery prior to 39 weeks (hypertensive disorder diagnosed prior to enrollment, gestational diabetes, multiple gestation)
- No fetal complication (e.g., birth defect, intrauterine growth restriction)
- No medical complication (e.g., chronic hypertension, preexisting diabetes mellitus)

Who do not currently ingest an over the counter probiotic supplement (not including yogurt)

Who can both speak and read English or Spanish

Pregnant women who regularly attend UNM prenatal clinics, First Choice Community Healthcare clinics, or Maternity and Family Planning Clinic for their prenatal care ("regularly attend" will be defined as starting prenatal care prior to 20 weeks gestation and missing no more than one prenatal appointment during this pregnancy)

No hypersensitivity reaction to β-lactam antibiotics

Exclusion Criteria

Those less than 18 years of age

Non-pregnant women

Later in pregnancy than 38 weeks gestation at enrollment [per LNMP and/or US]

Those with an obstetric, fetal or medical complication of pregnancy

Group B Streptococcus negative at 36 weeks gestation. Those ineligible for testing at 36 weeks gestation (history of GBS bacteriuria during the current pregnancy or have previously given birth to a GBS affected child.) We will not exclude those with bacteriuria other than GBS, and we will not exclude women who have taken an antibiotic during pregnancy, but we will track this as it is addressed in the Questionnaire for Participants.

Women who are currently ingesting an over the counter probiotic supplement (except for yogurt)

Women who are planning an elective repeat cesarean birth

Women who do not speak and read English or Spanish
Women who do not have electricity in the home.
Women with a history of missing one or more scheduled prenatal visit during this pregnancy
Hypersensitivity reaction to β-lactam antibiotics

Inclusion of Women: 100 percent of the outpatients making up our study population are women, which includes pregnant transgender/non-binary/gender non-conforming individuals.

Inclusion of Children: Children will not be included in this study.

Inclusion of Incarcerated Individuals: Incarcerated individuals will not be included in this study.

Inclusion of Minorities: We anticipate the racial-ethnic composition of the study sample to reflect that of the clinical population. If the proportion of minority women falls significantly below this anticipated number, we will consider targeted recruitment procedures to achieve the projected representation.

5. Number of Subjects

Up to 75 subjects seeking prenatal care at the University of New Mexico will be enrolled. Subjects will be pregnant, age 18 years or older, and registered as outpatients. Pregnant women are included because the purpose of this study is to determine the feasibility of studying the use of an oral probiotic agent in healthy, low risk, GBS positive pregnant women at term. We also propose to explore the effect of the probiotic on maternal GI symptoms and identify significant barriers to probiotic use in our population. Other special classes of subjects such as children, prisoners, and institutionalized individuals will not be enrolled.

This includes low risk patients seeking prenatal care at the University of New Mexico. Approximately 1500 women received prenatal care in the UNM Midwifery and OBGYN clinics in 2019 and approximately 20% were colonized with GBS. This gives us an adequate population from which to draw our study sample. We anticipate screening approximately 150 subjects over 8 months to allow us to enroll up to 75 subjects for our study after screening failures. A 30% dropout rate has been incorporated into sample size estimation to account for development of risk factors or failure to follow study procedures. These estimates are derived from Marquette University's randomized control trial pilot study of probiotics in pregnancy conducted at Marquette University and their current NIH funded double-blind randomized-controlled trial of Florajen3 to reduce GBS antenatal colonization. Tricore Lab has verified a 20% positive rate of GBS in our prenatal study population. For this open-label randomized control trial and feasibility study, a total sample of up to 75 participants will be targeted for enrollment and will be randomized to either the intervention group (receiving probiotics) or routine care (no intervention). A 30% dropout rate is assumed based on a preliminary study conducted at Marquette University; therefore, we anticipate that approximately 50 participants will

complete the study.

6. Study Timelines

Procedures and Timing: Data will be collected for all subjects at five time points: T1 baseline (36.0-37.6 weeks), T2 (on labor admission), T3 (postpartum day 0-14), T4 (2 weeks postpartum), and T5 (6 weeks postpartum) as indicated in the table below.

Following informed consent, participants will have their first study visit at 36.0-37.6 weeks gestation (T1), during which baseline data will be collected and each subject will complete several brief questionnaires. Participants will be randomized into intervention group or routine care. The research staff member will sequentially distribute one pre-labeled bottle of 30 probiotic capsules to the intervention group at time of enrollment. The bottle number will be used as the subject's number for the remainder of the study. Subjects in the control group will not receive any capsules and will be advised to continue their routine prenatal self-care. All subjects in the intervention group will be instructed to keep the study bottle in the refrigerator and to take one capsule per day until they give birth and to bring the bottle with them to the hospital at the time of labor. The PI, co-investigators, research staff, prenatal providers, and the subjects will not be blinded to group assignment.

The GBS vaginal to rectal swab collection procedure will be repeated for the both the intervention and routine care groups at T2 on labor admission. All participants will receive routine IAP per protocol as per CDC guidelines. At T3, the research staff will complete data collection with every participant during postpartum days 0-14; this will involve counting any remaining capsules in the study bottle, administering the study questionnaires, providing each subject with the first thank you merchandise card, and conducting a record review to document birth characteristics and IAP treatment. Adverse events will be solicited at each prenatal visit and via formal questionnaire for participants at T3-T5. Adverse events will be solicited at each prenatal visit and via formal questionnaire at T4-T5 for the newborn(s). A second merchandise card will be provided at T5.

Summary of Study Data Collection, Variables, Measures, and Timing

Outcome Variables	**Study Data Collection** Research staff will document data from all measures on the Summary Data Collection Form.	**T1** Baseline 36-37$^{6/7}$	**T2** Admission to L&D	**T3** Postpartum Day 0-14	**T4** 2 weeks postpartum	**T5** 6 weeks postpartum
	Procedures					
Qualitative GBS Colonization (+ or -)	Vaginal-rectal GBS swab.		X			
Intervention Adherence [Probiotic group only]	Final Capsule Count			X		
Maternal GI Symptoms	Antepartum Gastrointestinal Symptom Assessment (AP-GI-SA-10)	X		X		

Adverse Events	Adverse Event Solicitation and Documentation Form [Prenatal providers will also solicit for adverse events at all prenatal visits between study visits]			X	X	X
Demo-graphics	Demographic Questionnaire	X				
Lifestyle practices: sexual, hygiene, diet	Questionnaire for Participants	X		X		
Future Feasibility Form						X

Timeline for Completion of the Project

June 2020	-IRB submission -Planning for meetings with division partners (nursing, medical assistants, midwives, OBs, lab) -Create recruitment tools, handouts, posters -Complete translation of all study materials into Spanish -Upload all final questionnaires into the UNM REDCap system, study project. -Establish safe storage procedures for probiotics prior to distribution to participants -Request probiotic shipment from Florajen
July/August 2020	-Work with research staff and clinical partners on protocols for the 2nd GBS swab collection at T2 -Establish protocols for testing and billing of T2 study swabs with UNM Tricore lab -Receive probiotics from Florajen -Orient research staff to project & create parameters for EHR use for tracking patients -Present study at division meetings of partners (residents, clinic staff, faculty, L&D staff, lab) -Receive iPads from Marquette and add data collection forms to the UNM REDCap system.
September 2020	Start recruitment and data collection
April 2021	End recruitment
May 2021	-Final data collection -Begin data analysis in collaboration with Marquette University
May-September 2021	-Data Analysis -Submit for poster presentation at professional conference(s)
Fall 2021	-Grand Rounds Presentation -Development of poster presentation -Write a paper and submit for publication in peer reviewed journal

7. Study Endpoints

Our primary outcome variable is qualitative GBS colonization (positive versus negative), at the time of labor admission.

Secondary outcomes include intervention adherence, maternal gastrointestinal (GI)

symptoms, and maternal and infant adverse events, at the 6 week postpartum visit.

8. Research Setting

The study will be performed at the University of New Mexico (UNMH) Women's Care Clinic, Women's Health Clinic, First Choice Community Healthcare clinics, and Maternity and Family Planning Clinic. Potential subjects will be screened and recruited in the UNMH clinics. After recruitment, they will undergo the consent process, and fill out initial questionnaires in the outpatient offices or over the phone. Upon labor admission to L&D, a GBS swab will be taken for study participants in addition to what is routinely collected for standard of care. There will be no involvement of any community advisory board. There will not be any research conducted outside of the UNM HSC.

9. Resources Available

Katrina Nardini, CNM fills a leadership role in the Department of OBGYN as the Associate Chief of the Midwifery Division. She has completed a Master's in Public Health and has conducted a successful research project, submitted through the UNM IRB This study resulted in a published manuscript in the Journal of Midwifery and Women's Health. In addition, the topic of this current research project was her Master's Thesis work for her Masters of Science in Nursing. She regularly lectures at the College of Nursing on the topic of GBS. Noelle Borders, CNM will serve as a co-investigator for the current study. As a member of the Midwifery Division, Ms. Borders has collaborated on various studies including her role as co-investigator for the UNM APPLE study. She also collaborated on a recent study with Tricore lab, and has an excellent working relationship with the lab, who will work with us on this study. The other UNM co-investigators are part of the Midwifery Division and have collaborated on various studies with the OBGYN Department and Midwifery Division. We will also use the assistance of a medical student on our research team, who has participated in research studies in the past.

The University of New Mexico team will be collaborating with Marquette University, and have an approved DUA (FP00009196) to formalize the relationship. Marquette University has done extensive research on probiotic use and its effect on GBS. Researchers at Marquette University are currently conducting a phase 2 double-blind placebo-controlled trial of Florajen3 against GBS under Investigational New Drug (IND) #16549 and with NIH/NICHD funding 1R21HD095320-01; Project Period: 07/20/2018 –06/30/2020. This study is registered on clinicaltrials.gov NCT03696953. Marquette University submitted the IND for Floragen Digestion and will continue to work with and guide the UNM team on this project.

Research Experience: The research team in the OBGYN Department at UNM has a strong history of conducting high quality research and collaboration with other investigators in the US and abroad and has consistently met or exceeded recruitment goals on time. We have met recruitment goals with high rates of follow-up and accurate data collection.

Our group is well versed in the importance of adherence to protocols, timely completion of regulatory requirements, effective recruitment strategies, and the importance of the inclusion of minority subjects. Research is integral to all aspects of Divisional work; importantly, all members of the clinical team participate in research efforts. There are weekly research meetings to discuss the progress of the ongoing studies within the department, and it is an excellent forum to ensure that all involved are adequately informed of their duties, of the protocol, and of the procedures.

We do not anticipate that emergency care will be needed for this study, however the Midwives are available on a 24-hour basis, 7 days per week for their patients requiring emergency care.

10.Prior Approvals

There will not be any approvals obtained prior to commencing the research. The study was presented for approval by the Department Chair or Vice Chair of Research. The signed Departmental Review form can be found in the local site documents.

This study does not include any ionizing radiation.

The drug attachment form have been included in our Huron submission.

11.Multi-Site Research

N/A

12.Study Procedures

Participant flow through the study: Healthy adult pregnant women, who are GBS positive, at ≥ 36 weeks gestation, will be introduced to the study. If they express an interest in the study, the research coordinator will conduct a prenatal chart review after their GBS swab result has returned and review study inclusion and exclusion criteria for each interested woman by completing the Prenatal Eligibility Screening Form (PESF). For a woman who is eligible and willing, the research coordinator will complete the informed consent. Participants will provide written or e-signed consent at 36.0 to 37.6 weeks gestation. Consented participants will be randomized to one of two groups, standard of care/control group or the intervention group. Participants in the intervention group will begin taking oral study capsules once daily from time of enrollment/randomization at ≥ 36 weeks gestation until the time of birth. The research staff member will sequentially distribute the pre-labeled bottles of study capsules to the intervention group, one bottle of 30 Florajen Digestion probiotic capsules to women in the intervention group at the time of randomization. Because women are seen on a

weekly basis in late pregnancy, generally we anticipate that participants will receive the probiotic at enrollment; their next regularly scheduled prenatal appointment at approximately 37 weeks gestation. For women who do not attend this appointment in person, research staff can also arrange to meet participants at the prenatal clinic site to initiate the intervention between prenatal appointments. This will be arranged at the woman's convenience. Subjects in the control group will not receive any capsules and will be advised to continue their routine prenatal self-care. All subjects in the intervention group will be instructed to keep the study bottle in the refrigerator and to take one capsule per day until they give birth and to bring the bottle with them to the hospital at the time of labor.

All participants will complete baseline forms: Antepartum Gastrointestinal Symptom Assessment (AP-GI-SA-10), Demographic Questionnaire and the Questionnaire for Participants.

Research coordinators will be filling out a Summary Data Collection Form (SDCF) on all study participants.

At the time of labor admission to Labor and Delivery, participants will receive a vaginal-rectal GBS swab as a part of the research study. This is not standard of care and thus participants will receive this in addition to the standard of care. The results of the GBS swab will be collected for study purposes only.

All participants regardless of group assignment will receive the usual standard of care for GBS positive status and will be given intrapartum antibiotic prophylaxis (IAP) per protocol during labor.

All participants on postpartum day 0-14, in the hospital will answer these questionnaires: Antepartum Gastrointestinal Symptom Assessment (AP-GI-SA-10), Adverse Event Solicitation and Documentation Form (only for themselves, not their newborn(s)) and Questionnaire for Participants.

*we will not collect Adverse Event Solicitation and Documentation during this study time point because if the information is collected on postpartum day 0, there would be no way of reporting an adverse event for the newborn(s) at this time.

For the intervention group on postpartum day 0-14, study staff will conduct a final capsule count.

All participants at their 2 weeks postpartum visit will have an Adverse Event Solicitation and Documentation Form completed which will also include Adverse Event Solicitation and Documentation for their newborn(s).

All participants at their 6 weeks postpartum visit will have an Adverse Event Solicitation and Documentation Form & Future Feasibility Form completed which will also include Adverse Event Solicitation and Documentation for their newborn(s).

13. Data Analysis

Demographic characteristics for the full sample and each group will be presented. Logistic regression will be used to identify if the group assignments have relationships to variables such as demographic characteristics, hygiene practices, adherence, and birth characteristics. Logistic regressions test if any of these variables can predict the group that the participants were in. Another advantage of logistic regression is that by adding all the predictors at the same time, we can state the effect of each one controlling for the other predictors, presenting a stronger test of group independence.

For the continuous variables measured more than a single time (i.e. GI symptoms) the data analysis method will be latent change score model (LCM). This allows us to estimate the mean and standard deviation of the change between time points. By adding the group into the LCM, we will test the group mean difference in the change over time between the treatment and placebo groups. This will test the significance and clinical relevance (effect size) of the treatment over time. For the binary variable (qualitative GBS colonization), we will use logistic regression, with the baseline GBS colonization and treatment group as predictors. This would allow to test differences in the likelihood of being GBS positive, controlling for their initial status. The clinical relevance can be evaluated with the effect size Odds Ratio. For all the analyses, relevant demographic characteristics, hygiene practices, adherence, and birth characteristics identified in the first step will be added as covariates, to account for their possible influence in outcomes of interest.

14. Provisions to Monitor the Data to Ensure the Safety of Subjects

Risk Management and Emergency Response. If any study participant has a fever or other signs of infection, they will be instructed to contact the clinic or OB Triage, as is the usual process for pregnant women. Subjects will be provided with the PI contact information in the event that they need to call after hours. In the case of emergency, such as severe illness, the subjects will be instructed to call OB Triage and seek care in the University of New Mexico system whenever possible. Patient participation in the research study will be noted in the antenatal problem list; any healthcare provider who cares for the patient will have knowledge of study participation. Although highly unlikely, if it is determined that a subject has a clinical infection due to any component of Florajen Digestion Howaru® Dophilus-Lactobacillus acidophilus NCFM™; Lactobacillus acidophilus La-14; floraFIT Bifidobacterium lactis Bi-07™; Bifidobacterium animalis ssp. Lactis HN019, floraFIT Bifidobacterium longum Bl-05™, as determined by culture and strain-typing, standard medical care will be provided to

the subject. No such emergencies occurred during the pilot testing or during NIH/NICHD funding R21HD095320 that is in progress under IND#16549 at the time of this application.

Adverse Event Monitoring: Providers will solicit for adverse events at every patient encounter that are not pregnancy related. Katrina Nardini, CNM, MPH will be alerted if any unexpected adverse event occurs, to determine whether changes in the study protocol (e.g., additional safety measures, change in exclusion criteria) are needed. If any changes to the protocol are needed, Katrina Nardini, CNM, MPH will notify the UNM IRB. Approval of the IRB is necessary prior to introducing any modifications to previously approved protocols that involve human subjects. The PI and the research team will meet monthly to review study progress, including any adverse events. In routine postpartum follow up (T4 and T5), study participants will also be solicited for adverse events. Safety reports will be reviewed monthly by reviewing the data collected on the adverse events questionnaires. The literature will be reviewed on a quarterly basis. One formal interim analysis of efficacy will be performed by a biostatistician at approximately 50% of the total information fraction. A two-sided O'Brien-Fleming boundary will be utilized in conjunction with a Lan-DeMets spending function to assess whether the intervention is showing a much stronger or weaker effect on outcomes than expected. If this occurs, the PIs and research team will give consideration to stopping the trial early. Summary reports of interim analyses will be provided to the funding agency. In the event of suspension or early stopping of the trial, the Human Subjects Protection Program Offices and funding agency grant program official will be promptly notified.

Special Situations: Pregnancy. Marquette University and colleagues have rigorously reviewed the literature on prenatal probiotics in preparation for the proposed study. According to the integrative review of the literature (VandeVusse, et al., 2013; Appendix A.2.), and systematic review and meta-analysis of probiotics against GBS in progress, probiotic agents have been safely used in pregnancy in more than 50 published clinical trials without adverse events to the mother or the fetus. Florjen3 has been used in a pilot study in which 10 pregnant women took this same probiotic once daily orally from 28 weeks through 36 weeks and in a randomized control trial (RCT) conducted under IND#16549 with NIH/NICHD funding 1R21HD095320. No adverse events or negative side effects have been solicited from participants in either study.

15.Withdrawal of Subjects

Any participant may withdraw from the study at any time without penalty and will continue to receive the clinical standard of care. Data collected until that point will remain in the study database and may be used for data analysis. A subject may be withdrawn from the study without her consent at the discretion of the midwife and study staff if they believe she no longer meets study inclusion criteria or if she meets exclusion criteria, or if they believe that it is not in her best interest to continue study participation.

Investigators may withdraw a subject if the subject is not following the study protocol. If a woman is withdrawn from the study either at her own discretion or that of the research staff, she may continue with the standard of care performed in the usual fashion.

To minimize withdrawal from the study, patients will be enrolled and randomized only after confirmation of meeting eligibility criteria. According to the 2010 CONSORT guidelines, we will analyze all participants assessed for eligibility within the study. We will document and report eligibility criteria not met or reasons for declining participation in the study. We will also document reasons for withdrawal from the study if the patient has been enrolled and later revokes consent to participate in the study. The withdrawal procedure is clearly documented in the study consent.

16.Data Management/Confidentiality

A limited data set of data will be shared with Marquette University per the Data Use Agreement in place. Subject ID will be assigned based on order of enrollment in the study. Randomization assignment will be generated by a computer based randomization table and assigned by a research coordinator. Assignments will be made through the REDCap database. All data collection sheets and questionnaires will contain the subject number and day of the clinic visit. PHI including patient name, date of birth, phone number, and medical record number will need to be collected to track for appointments. No other patient identifiers will be collected aside from those listed above.

The data collection, HIPAA and consent forms will be maintained in a locked file cabinet in the OBGYN administrative area. A separate folder will be designated for each participant. Data will be kept separately from study records containing patient identifiers. The offices have the additional security of being badge-access only for OBGYN department employees. A key matching study number to subject's name will be in a spreadsheet secured on a password protected computer separate from study data. The only PHI collected will be patient name, date of birth, medical record number and telephone number for site use only and to ensure patient follow up. This will not be entered into the database, but it will be kept with the other identifying information. The data does not include sensitive information or information requiring additional protection. Data will be entered into REDCap either directly by the study participants using study iPads or by the research team for participants who complete the questionnaires by phone or in clinic. The iPads will be stored in the locked OBGYN administrative offices. The electronic data will be encrypted, password protected, and stored on the secure UNM OBGYN department server. This server's electronic security is monitored / maintained by the Health Sciences Library and Informatics Center (HSLIC). A REDCap database will be created to collect, store and manage the data. REDCap databases are reposed securely. The REDCap database is only accessible using an individual unique login and password and access is only provided to co-investigators. Access is restricted to co-investigators and will be protected using the unique REDCap login and password provided to each co-investigator. Access

to the files and REDCap will be restricted to research personnel and Investigators and will be locked or protected using the unique REDCap login and password provided to each co-investigator. The data will be stored for 6 years after completion of the study and then will be destroyed. Data collected on neonates, which will be the adverse events, will be stored for 22 years after completion of the study and then will be destroyed.

A Certificate of Confidentiality will not be used to protect data from forced release.

Data will not be shared with Marquette University without a Data Use Agreement in place.

17. Data and Specimen Banking

GBS swabs will be labeled by subject ID on study specific Tricore requisition forms, Tricore will process and dispose of them following their standard procedures. Results will be sent to study PI and research staff.

18. Risks to Subjects

Physical Risks. Study vaginal-rectal swabs will be collected with a cotton tipped swab without the need for a speculum on labor admission. As per current protocol for GBS collection, study participants may self-collect this swab. This may pose minor discomfort to subjects.

Physiologic Risks.. No physiologic risk

Social Risks. The social risk is that of a possible breach of confidentiality regarding the health information of subjects. Research data will be handled with utmost confidentiality and discretion. Each participant will be assigned a unique identification number that can be traced only by the research staff. All subject information will be kept in locked drawers of file cabinets and/or secure password protected computer files, with access only allowed to research personnel. Only IRB approved research personnel will have access to PHI.

Ethical, Psychological, Legal, and Other Risks. The Questionnaire for Participants contains information about specific sexual and vaginal cleansing practices. Sharing this information may make women feel uncomfortable or embarrassed. These completed questionnaires will be marked with only the subject's study number and will be placed in a sealed envelope by the participant when completed, then collected by the research staff; these data will not be a part of the prenatal record. All participants will receive prenatal care according to the accepted standards of care, including universal prenatal screening for GBS at 36 weeks gestation, according to the CDC (2010)/ACOG (2019) update. Participants will be informed of this prenatal GBS culture result by their providers and IAP will be administered to all subjects as indicated by this required prenatal GBS result. Additional sample swabs done for study purposes on admission for labor and birth and

their results will not be available to the prenatal providers. This will be clearly stated in the consent form. If, during the course of the study, new data in the literature emerge suggesting that interventions to routinely reduce GBS are beneficial, then care will be revised to ensure good clinical care for all participants.

The probiotics included in Florajen Digestion are "Generally Regarded as Safe" (GRAS) and are included in infant formulas. There are numerous studies of the use of probiotic interventions in sick and premature infants especially for the prevention of necrotizing enterocolitis (1). There have been no adverse events found in neonates born to mothers exposed to antenatal probiotics such as those included in Florajen Digestion. The systematic review and meta-analysis concerning antenatal probiotics administration suggest benefits such as a decrease in atopic disease in offspring (2).

1.Patel RM, Underwood MA. Probiotics and necrotizing enterocolitis. Semin Pediatr Surg. 2018;27(1):39-46. doi:10.1053/j.sempedsurg.2017.11.008

2.Li L, Han Z, Niu X, Zhang G, Jia Y, Zhang S, He C. Probiotic Supplementation for Prevention of Atopic Dermatitis in Infants and Children: A Systematic Review and Meta-analysis. Am J Clin Dermatol. 2019 Jun;20(3):367-377. doi: 10.1007/s40257-018-0404-3. PMID: 30465329.

There is a possibility of unforeseen risks.

19.Potential Benefits to Subjects

The potential benefits to research subjects associated with this study include the possible reduction in colonization with GBS. A benefit may be seen if any hypothesis of the study is supported. In this case, any benefit would be a direct benefit only to the subjects receiving the study probiotic, Florajen Digestion. If, as we hypothesize, the probiotic Florajen Digestion is beneficial in reducing GBS colonization, the probiotic study participants may benefit in lower rates of resulting comorbidities.

This is a feasibility study to assess whether this intervention is acceptable in our population. Our hope is that a larger future study may then show a decrease in prenatal colonization with GBS, and that the community at large could benefit by gaining an alternative therapeutic option to reduce early onset Group B streptococcal disease and other related comorbidities. Identification of a novel non-antibiotic based strategy, such as a probiotic, to reduce GBS offers considerable benefit to society.

20.Recruitment Methods

A sample of 75 low risk, English or Spanish speaking, healthy adult pregnant women who are GBS positive, at ≥ 36 weeks gestation, will be recruited from certified nurse-midwife and physician panels at the University of New Mexico (UNM) prenatal clinics, the First Choice Community Healthcare clinics, and Maternity and Family Planning Clinics. Participants will begin the study at 36.0 to 37.6 weeks gestation. To facilitate recruitment, there will be posters displayed in the waiting areas and in each prenatal examination room, as well as recruitment brochures available. The poster and brochure

will be added to the study record for HRRC approval through a modification. The research coordinator will work with the clinic receptionists, staff, and providers to identify women at ≥ 36 weeks gestation on the day of their prenatal visit to the clinic. Recruitment will also be aided by using Tricore's CTSC Data Warehouse to identify pregnant people who test positive for GBS. A message will be sent via Powerchart (secure) to the PI of patients with GBS positive results; the PI and IRB approved research study team will review the chart for eligibility and participants approached regarding interest in the study. Tricore's CTSC Data Warehouse is not the same entity as First Choice Community Healthcare or Maternity and Family Planning. Once identified and introduced to the study, potential participants will be provided with a copy of the informed consent document and informed that they may be eligible to participate in the study if they are found to be GBS positive. If a woman expresses interest in the study, the research coordinator will conduct a prenatal chart review to determine the GBS result. If a woman tests positive, the research coordinator will review study inclusion and exclusion criteria by completing the Prenatal Eligibility Screening Form (PESF). The research coordinator will then call the woman, thank her for her interest, and indicate whether she meets the study eligibility criteria. For a woman who is eligible and willing, the research coordinator will complete the informed consent procedures and collect written e-consent. All study team members screening participants have access to HIPAA information as part of routine clinical care.

21. Provisions to Protect the Privacy Interests of Subjects

Privacy concerns are taken into account with every patient seen at the UNM. Participants approached and/or interviewed in the clinic setting will be in private offices or examination rooms in the UNM clinics, First Choice Community, or Maternity and Family Planning Clinics Healthcare clinics, where all staff, including research staff, are well-versed in sensitive health care discussions and procedures. Telephone interviews for recruitment and study data gathering are conducted in the research staff area or private physician offices, where all staff have received CITI Training. The office area designated for the entire research staff is isolated from the clinical administrative staff area, providing protection for participants and potential participants during screening, recruitment, study-designated calls, and data entry.

All study sheets used to collect patient information will contain limited data.

At all times throughout the clinical investigation confidentiality will be observed by all parties involved. All data will be secured against unauthorized access. Privacy and confidentiality of information about each subject will be preserved in study reports and in any publication. Each subject participating in this study will be assigned a unique identifier. HIPAA authorization is within the consent. All documents containing personal health information (screening logs, consent documents, data forms) are maintained in locked file cabinets with access available only to research staff and investigators. Data is entered into a password-

protected system. No individual identifiers are entered into the system. The sole link with personal information is maintained by the research team on a password protected computer on a secure UNM OBGYN department server with access limited to authorized research staff and investigators.

22. Economic Burden to Subjects

Research Procedures	Number of Samples/Procedures	Responsible Party	
		Study	3rd Party Payer or Participant
Probiotics (intervention group only)	30	☒	☐
Intervention Adherence- pill count	1	☒	☐
Antepartum Gastrointestinal Symptom Assessment (AP-GI-SA-10)	2	☒	☐
Adverse Event Solicitation and Documentation Form	3	☒	☐
Demographic Questionnaire	1	☒	☐
Questionnaire for Participants	2	☒	☐
Vaginal-rectal GBS swabs	1	☒	☐
Future Feasibility Form	1	☒	☐
Standard of Care Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
		☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐

GBS swabs taken on L&D and the merchandise cards that participants will receive for their participation in the study will be funded by the Department of OBGYN Curet Research Grant of $10,000. Dr. Hanson has also provided two iPads with $1000.000 funds from her research endowment.

23. Compensation

Participants will receive up to a total of $40 merchandise card. Participants will receive a $20 merchandise at the time of postpartum day 0-14 and then a $20 merchandise card at completion of the 6 week postpartum visit.

24. Compensation for Research-Related Injury

If participants are injured or become sick as a result of this study, UNM HSC will provide emergency treatment at the study participant's cost. No commitment is made by the University of New Mexico Health Sciences Center to provide free medical care or money for injuries to participants of the study. Reimbursement for treatment for all

related costs of care will be sought from the participant insurer, managed care plan, or other benefits program. The participant will be responsible for any associated copayments or deductibles required by the insurance. Participants will be asked to report any illness or injury they believe to be related to the study to the investigator or research staff. Participants will be given telephone contact information for the midwives 'office for the purpose of asking any questions or stating any concerns about the study or treatment as a research subject. They may also be directed toward the HRPO. This language will be stated in the written consent document and reviewed during the informed consent process. There is no additional risk to participate in this study.

25.Consent Process

Patients will be approached about the research study in the UNM prenatal clinics at the Women's Care Clinic, Women's Health Clinic,First Choice Community Healthcare clinic, and Maternity and Family Planning clinic. The study will be introduced by providers at the time of routine GBS swab collection and written information will be provided. Once identified, each GBS positive woman will be approached by a study team member, if interested the study consent will be obtained by one of the research team members. Additionally, care will not be withheld if they decide not to participate.

The research staff will be responsible for the informed consent process, including discussion of the study and the subject's role in the study, and for answers to any questions posed by the subject. Once the subject indicates understanding, comprehension will be verified by asking the subject to explain the basics of the study, including the participant's role and possible risks and benefits. The informed consent will be signed or e-signed by the participant and the research coordinator. A copy of the signed or e-signed consent will be given to the participant and a copy will be securely stored by the research coordinator. Patient participation will be noted in the electronic medical record antenatal problem list in order to identify participants for collection at the time of labor.

They will have multiple opportunities to ask any questions that they may have, and they will also be provided with the clinic's contact information to get in touch with research investigators to address any additional questions or concerns.

Subjects will be reassured that participation is completely voluntary and does not affect their treatment, their relationship with their providers, or the university to minimize the possibility of coercion or undue influence. The patients will be asked that they understand the opportunity to participate and their complete freedom to decline. This will also be asked if they understand and if they have any questions. There is no minimum time period needed between informing the patient of the study and time of consent. Subject will be encouraged to take as much time as they need.

This study will obtain HIPAA authorization prior to enrollment. HIPAA authorization is embedded within the study consent form, which will be reviewed with all participants by the study team member(s) obtaining consent. Specific information that will be obtained includes data on demographics (socioeconomic status, race and ethnicity), lifestyle

practices (sexual practices, hygiene, and diet), and birth characteristics (mode of birth, whether the membranes were ruptured or not prior to the GBS swab, birth weight, birth length, head circumference, Apgar scores at 1, 5, and 10 minutes, which are all included in the maternal medical record).

Spanish speaking patients will be included. We will submit the translated documents once the study is approved by the IRB.

Cognitively Impaired Adults will not be included in the study.

All subjects will be 18 years of age or older. No infants, children, or teenagers will be enrolled in the study.

26.Documentation of Consent

We plan to document consent, and the Consent form is attached. We do not plan on collecting/storing tissue samples. GBS is not a tissue sample, but a test to screen for a bacterium. We will obtain written or e-signed consent to aid in limiting in-person contact due to the pandemic. We will not be using a script, information sheet, or other mechanism. The eConsent will be collected via the UNM HSC REDCap system or via email depending on the participant's capabilities.

27.Study Test Results/Incidental Findings

We do not intend to share study test or procedure results with study participants. Additionally, we do not anticipate that the research being conducted will result in incidental findings. Every patient will receive the practice's standard of care as determined by their other active medical issues. These results are not part of the research being conducted and will hence be disclosed to the patient as appropriate for standard of care.

28.Sharing Study Progress or Results with Subjects

The patients will not be masked to their study arm. We do not intend to seek out study participants to disseminate information once the study is complete. Women who are interested in the results will be provided the information where to read the manuscript once it is published. Study results for individual participants will not be shared.

29.Inclusion of Vulnerable Populations

This research includes pregnant women. Those electing to participate will not be subject to coercive recruitment/data collection methods.

30.Community-Based Participatory Research

N/A

31. Research Involving American Indian/Native Populations

NA. This research does not specifically target this population. If a Native American woman is a candidate for this study, she will be offered participation.

32. Transnational Research

N/A

33. Drugs or Devices

An FDA Investigation of New Drug Application was submitted May 18, 2020 & has been approved (IND # is 22834). Marquette University holds an FDA IND for the highly similar product Florajen3 that is no longer manufactured.

Florajen3, currently used in Marquette University's clinical trial, is no longer manufactured. Therefore, for our research we will use Florajen Digestion as the intervention. Compared with Florajen3, Florajen Digestion has two additional probiotic species. Florajen Digestion is a probiotic combination product composed of freeze-dried strains of live organisms, including Howaru® Dophilus-Lactobacillus acidophilus NCFM™; Lactobacillus acidophilus La-14; floraFIT Bifidobacterium lactis Bi-07™; Bifidobacterium animalis ssp. Lactis HN019, floraFIT Bifidobacterium longum Bl-05™ for a total 15 x109 CFU per capsule. In vitro testing (Ephraim et al., 2012; Appendix A.2.) demonstrated that the live culture, freeze-dried, probiotic combination Florajen3 inhibited GBS when they are cultured together. In vivo pilot testing of Florajen3 was completed in early 2012 in an open-label, randomized control trial study with 10 pregnant women taking the probiotic capsule daily and 10 serving as controls (Hanson et al., 2014; Appendix A.1.). Findings suggested that the probiotic intervention suppressed growth of GBS. Women in the probiotic group reported no side effects.

Probiotics will be stored in a refrigerator in the research office.

34. Principal Investigator's Assurance

By submitting this study in the Click IRB system, the principal investigator of this study confirms that:

☒ The information supplied in this form and attachments are complete and correct.

☒ The PI has read the Investigator's Manual and will conduct this research in accordance with these requirements.

☒ Data will be collected, maintained and archived or destroyed per HSC Data Security Best Practices, including:

1. **Best Practice for data collection** is for it to be directly entered onto a data collection form that is in a secured access folder on an HS drive behind a firewall, or in a secure UNM Data Security approved system such as RedCap.

2. **Data collection of <u>de-identified data</u>**, if done in a clinical setting or other setting that does not allow direct entry into a secured system, may be done temporarily using a personal or university owned electronic storage device or hard copy document. **The important security safeguard is that no identifiers be include if the data is entered or stored using an untrusted device or storage.**
3. **Permanent (during data analysis, after study closure**) storage must reside on HSC central IT managed storage. Processing of data (aggregation, etc.) are to be carried out in such a way as to avoid creating/retaining files on untrusted storage devices/computers. Trusted devices are HSC managed and provide one or more of following safeguards: access logs, encryption keys, backups, business continuity and disaster recovery capabilities.
4. **Alternate storage media** must be approve by HSC IT Security as meeting or exceeding HSC central IT provided security safeguards.

35.CHECKLIST SECTION

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

36.Vulnerable Populations (Checklist)

A. Pregnant Women and Fetuses

Complete this checklist if the subject population will include pregnant women and fetuses.

This checklist does not need to be completed if the research is both minimal risk and is not conducted, funded, or otherwise subject to regulation by DHHS, DOD, EPA, or VA.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.

   The safety and tolerability of probiotics in pregnancy has been documented over decades of international research. Previous trials using probiotics have been used in numerous studies involving pregnant women, and there have been no adverse events reported (please see background section of this protocol for reference to these trials).

2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; ***or***, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

   There may be potential benefits to the woman and/or her fetus, as there are documented benefits of probiotic use. The risk to the fetus appears minimal. Previous trials using probiotics have been used in numerous studies involving pregnant women, and there have been no adverse events reported (please see background section of this protocol).

3. Any risk is the least possible for achieving the objectives of the research.

   There is minimal risk to using probiotics, with potential benefits. Additionally, women already receive a GBS swab as part of their prenatal care, so by subjecting them to a second swab, they are not being placed at additional risk than what they already receive as standard prenatal care.

37.Specimen Transfer/Sharing (Checklist)

Complete this checklist if the research involves transferring/sharing of specimens with an external entity (institution, company, etc.).

A. Will specimens be transferred/shared with an external entity (institution, company, etc.)?

☐ Yes

☒ No. **The remainder of this section does not apply.**

B. Indicate if the specimens are incoming and/or outgoing:

C. Provide the name of the entity that specimens will be being transferred/shared with:

D. Provide the contact name, email and phone number with whom specimens are being transferred/shared with:

E. Who is responsible for sending out the specimens? Please note specimens cannot be sent out without a fully executed material transfer agreement.

F. Who is responsible for receipt of the specimens? Please note specimens cannot be received without a fully executed material transfer agreement.

G. For specimens being transferred/shared with outside locations or entities, describe the following:

- *Where is specimen storage and how will it be maintained in a secure manner?*
- *What is method in which specimens will be collected and stored?*
- *How long will the specimens be stored?*
- *Who will have access to the specimens?*

38.Data Transfer/Sharing (Checklist)

Complete this checklist if the research involves transferring/sharing of data with an external entity (institution, company, etc.).

A. Will data be transferred/shared with an external entity (institution, company, etc.)?

☒ Yes

☐ No. **The remainder of this section does not apply.**

B. Indicate if the data is incoming and/or outgoing: Outgoing

C. Provide the name of the entity that data will be transferred/shared with: Marquette University

D. Provide the contact name, email and phone number with whom data is being transferred/shared with: Lisa.Hanson@marquette.edu

E. Who is responsible for transmission of the data? *Katrina Nardini, CNM*

F. Who is responsible for receiving the data? *Lisa Hanson, PhD, CNM*

G. Describe how the data will be transferred/shared. Please note data cannot be transferred/shared without assistance from UNM HSC IT. **Requesting HSC Central IT Transfer is detailed on the Sponsored Projects website:** *UNM HSC Centeral IT provided network storage*

H. For data being transferred/shared with outside locations or entities, describe the following:
    - Where is data storage and how will it be maintained in a secure manner (i.e. encryption, password protection, use of Qualtrics or REDCap, etc)? Data will be stored on a password protected computer in a UNM secured, shared folder.
    - What is method in which data will be collected and stored (i.e. electronic, hard copy, etc)? *electronic*
    - How long will the data be stored? *Data will be stored for 6 years after the completion of analysis and then will be destroyed.*
    - Who will have access to data? *UNM IRB approved study team members and Marquette University study team.*

I. Please list all specific data elements, variables, etc. to be sent out and/or received. Indicate if the data contains identifiers and health information. Please note that identifiers that MUST be removed to make health information de-identified are as follows: Names, All geographic subdivision smaller than a State, All elements of year (except year), Telephone, Fax numbers, E-mail addresses, Social Security, Medical record number, Health plan beneficiary, Account numbers, Certificate/license numbers, Vehicle identifiers and serial numbers, Device identifiers and serial numbers, Web URLs, IP address numbers, Biometric identifiers, full face photographic images, and Any other unique identifying number, characteristic or code.) *Race, ethnicity, socioeconomic status, education and response to study questionnaires.*

J. If the research requires the access, use, or disclosure of any of the 18 individually identifiable protected health information (PHI) identifiers that can be used to identify, contact, or locate a person (e.g., name, medical record number, etc.), are the subjects going to consent to or authorize the disclosure of their individually identifiable health information? *Yes.*
    a. ***Or*** is HIPAA authorization altered or waived?

K. What is the classification of the data (de-identified, limited data set, protected health information, other). Limited data set

L. Does the request to transfer/share data include clinical data that belongs to the UNM Health Systems? Yes

M. Does the data to be transferred/shared include information about patients seen at external health system or at a third party medical provider? No

N. Is the external entity a "covered entity"? Yes

O. Is the data that is going to be transferred/shared owned or partially owned by another party or have any type of restrictions including regulatory restrictions (i.e. HIPAA, FERPA, etc.)? No

P. Is the data publically available? If yes, please provide details: *No*

Q. Does the data include information about substance abuse treatment, sexually transmitted diseases, genetic testing results, HIV/AIDS testing results, and/or mental health? No