STUDY PROTOCOL

MARANI PRENATAL **C**ONNECTED C**ARE** (M•care) **S**afety and **E**ffectiveness Study **(M•CARE SE Study)**

Protocol Number: MH-001

Revision: G
14-Dec-2022

NCT05294211

PROTOCOL AGREEMENT FORM

MARANI PRENATAL CONNECTED CARE (M•care) Safety and Effectiveness Study (M•CARE SE Study)

Revision G

I confirm that I have read the above-referenced protocol and understand its contents. The information it contains is consistent with the current risk-benefit evaluation of the investigational product.

I agree to conduct the study according to this protocol and to comply with its requirements, subject to scientific, ethical, and safety considerations. I will obtain the required Institutional Review Board (IRB) approvals prior to initiating the study and will abide by any additional requirements imposed by the IRB. I will provide copies of this clinical study protocol and all pertinent information to the study personnel under my supervision and will discuss this material with them and ensure they are fully informed regarding the investigational product and the conduct of the study. I agree to conduct the study in compliance with the Declaration of Helsinki, Clinical investigation of medical devices for human subjects – Good Clinical Practice (ISO 14155:2020 GCP), and applicable regulatory requirements.

I understand that modifications to the study are acceptable only with mutually agreed upon protocol amendments. Should I decide to withdraw from participating in the study, I will immediately communicate such decision in writing to the Sponsor.

_____

Clinical Site Name

_____	_____	_____
Site Principal Investigator (Print Name)	Site Principal Investigator (Signature)	Date

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL SYNOPSIS	
Study Title	**M**ARANI PRENATAL **C**ONNECTED C**ARE** (M•care) **S**afety and **E**ffectiveness Study **(M•CARE SE Study)**
Procedure Name	Antenatal Fetal Monitoring
Sponsor	Marani Health, Inc.
Protocol Number	MH-001
Objective	To demonstrate the safety and performance of the Marani Fetal Monitoring Telehealth System (M•care™ System) for use in antenatal monitoring of pregnant women ≥ 32 weeks' gestation. The M•care System will be evaluated by comparing Fetal Heart Rate (FHR), Maternal Heart Rate (MHR) and Uterine Contractions (UC) to Doppler FHR, Pulse Oximeter MHR, and tocodynamometer (TOCO) UC, respectively, measured with an FDA cleared standard of care cardiotocography (CTG) device.
Study Design	This is a multi-center, single arm, prospective paired comparison trial to determine the equivalence of the Marani M•care System with an FDA cleared Doppler FHR, TOCO UC and Pulse Oximetry MHR standard of care CTG device.
Duration	The expected monitoring duration for each subject is a minimum of 60 minutes and maximum of 120 minutes.
Study Device Description	Marani Health's M•care System is a fetal heart rate (FHR), maternal heart rate (MHR), and uterine activity (UA) monitoring system intended for home use by a pregnant woman as prescribed by their healthcare provider. The M•care™ System is comprised of 3 components: (1) The M•wrap™, a wearable compression abdominal band with an integrated electronics hub, called the M•core™, mounted to the garment, that interfaces with

	(2) the removable Orbital Research SilverBump dry electrodes and (3) mobile and web-based software applications to securely transmit subject vital data to secure systems Owing to the unique placement of electrodes within the M•wrap, the functionality of the system is not dependent on fetal position. The M•care System is being developed in accordance with the requirements of FDA's Quality System Regulation for Medical Devices, 21CFR Part 820, and ISO13485:2016 Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes. Both FDA and ISO 13485 mandate the use of Design Controls to ensure a formalized approach to development of medical devices. Marani Health has established Design Control procedures to ensure that a robust, and uniform product development methodology is being followed. This methodology includes, but is not limited to, the following requirements: • Design and Development Plans are established, reviewed, updated, and approved. • Design Inputs are identified to ensure that design requirements are appropriate and address the intended use. • Design Outputs are defined to allow for adequate evaluation of conformance to design inputs. • Design Reviews are planned and conducted at appropriate stages during development. • Design Verification is performed to ensure the design output meets the design input requirements. • Design Validation is performed to confirm that devices conform to defined user needs and intended uses under actual or simulated use conditions. The output of these activities is maintained in a Design History File in Marani Health's Quality Management System.
Reference Device	Philips Avalon FM20, Philips Avalon FM30, Philips Avalon FM40, or Philips Avalon FM50 (K140535) FDA cleared Doppler FHR, TOCO UC + Pulse Oximeter with a dedicated PC and cable connections. **Indications for Use for the Philips Avalon FM20, FM30 FM40 or FM50 reference device:** **Avalon Fetal/Maternal Monitor FM20:** Indicated for use by trained health care professionals whenever there is a need for monitoring of the physiological parameters uterine activity, heart rate, oxygen saturation, noninvasive blood pressure, pulse rate and temperature of pregnant women and the fetal heart rates of single fetuses,

	twins, and triplets in labor and delivery rooms, in antepartum testing areas, in private households and during transports in healthcare facilities. **Avalon Fetal/Maternal Monitor FM30:** Indicated for use by trained health care professionals whenever there is a need for monitoring of the physiological parameters uterine activity, heart rate, electrocardiography (ECG), oxygen saturation, noninvasive blood pressure, pulse rate and temperature of pregnant women and the fetal heart rates of single fetuses, twins, and triplets in labor and delivery rooms, in antepartum testing areas, in private households and during transports in healthcare facilities. **Avalon Fetal/Maternal Monitor FM40:** Indicated for use by trained health care professionals whenever there is a need for monitoring of the physiological parameters uterine activity, heart rate, oxygen saturation, noninvasive blood pressure, pulse rate and temperature of pregnant women and the fetal heart rates of single fetuses, twins, and triplets in labor and delivery rooms and in antepartum testing areas. **Avalon Fetal/Maternal Monitor FM50:** Indicated for use by trained health care professionals whenever there is a need for monitoring of the physiological parameters uterine activity, heart rate, electrocardiography (ECG), oxygen saturation, noninvasive blood pressure, pulse rate and temperature of pregnant women and the fetal heart rates of single fetuses, twins, and triplets in labor and delivery rooms and in antepartum testing areas.
Number of Sites	A minimum of 3 and up to 5 centers including: • Mayo Clinic (Rochester, MN) • NorthShore University HealthSystem (Evanston, IL) • St. Catherine's University (St. Paul, MN)
Countries	United States
Study Duration Per Subject	Expected duration of the study is approximately 3 hours for each subject. This includes study recruitment and data collection. This is typically a single-visit study; however, monitoring may occur during a separate visit after screening and consent have occurred.
Total Study Duration	The total expected study duration is 6 months.

Expected Study Enrollment	Plan to recruit up to 130 subjects in total across all sites resulting in a minimum of 80 evaluable subjects to achieve performance endpoints. No single site shall have greater than 50% of the patient recruitment population.
Study Population	Two study groups will be included in order to ensure collection of sufficient uterine contraction activity data. The study groups are as follows: • Antenatal – includes subjects evaluated per obstetric standard of care in the clinic/office environment and subjects completing research-only visits in a non-clinic setting with oversight by a healthcare professional. Subjects with premature rupture of membrane (PROM) will also be included. • Enriched Hospital – includes subjects in early (latent) phase of labor with suspected or confirmed uterine contractions, and subjects who are being induced for labor. For all analyses, the combined Hospital and Antenatal groups will be considered the Primary Analysis Population. Additional supportive analyses will be conducted for each study group separately. An effort will be made to include subjects in each Body Mass Index (BMI) stratum. BMI measurements are pre-pregnancy. **Hospital Group:** • Subjects with a (BMI) ≤ 29 • Subjects with a BMI > 29 but ≤ 35 • Subjects with a BMI > 35 but ≤ 45 **Antenatal Group:** • Subjects with a Body Mass Index (BMI) ≤ 29 • Subjects with a BMI > 29 but ≤ 35 • Subjects with a BMI > 35 but ≤ 45
Inclusion Criteria	Subjects eligible for this clinical study must fulfill **all** of the following criteria: 1) Able to provide Informed Consent and follow study instructions 2) 18 years of age or older 3) Pregnant subjects ≥ 32 weeks' gestation 4) Singleton pregnancy 5) BMI ≥15, pre-pregnancy 6) BMI ≤45, pre-pregnancy 7) Belly circumference ≥80 cm and ≤ 135 cm NOTE: Subjects admitted for induction of labor and subjects being monitored for premature rupture of membranes (PROM) or other inpatient evaluations can be enrolled in the trial.

Exclusion Criteria	Subjects are not eligible if **any** of the following criteria are met: 1) Known major fetal malformation or chromosome abnormality 2) Abdominal medical skin conditions, including surgical incisions, open wounds with or without infections, edema, or irritation 3) Subjects with implanted electronic devices (pacemakers, defibrillator, etc.) 4) Involvement in another clinical trial currently or previously in this pregnancy that, in the investigator's opinion, would affect the conduct of this study. 5) Medical or obstetric problem that in investigator's opinion would make the subject incapable of taking part in the study. 6) In the investigator's opinion, the subject is not likely to be available for the minimum 60 minutes of the monitoring session. 7) History of skin allergies to cosmetics and lotions. 8) Known allergies to silver, nylon, or polyester. *Note: some people with sensitivity to silver jewelry are sensitive to the impurities in silver alloys and not to silver itself.*
Primary Performance Measures	• Fetal Heart Rate (FHR) as measured by the M•care System versus standard of care CTG device. • Maternal Heart Rate (MHR) as measured by the M•care System versus the standard of care CTG Pulse Ox.
Secondary Performance Measures	The secondary performance measure is Uterine Contractions (UC) sensitivity as measured by the M•care System versus the standard of care CTG device. Hypothesis testing for UC sensitivity will only be conducted if the primary performance measures (i.e., equivalence in FHR and MHR) are met. Additional UC endpoints as measured by the M•care System versus standard of care CTG device include: • Positive predictive value (PPV) • False Positive Rate No hypothesis testing is planned for the PPV and false positive rate endpoints.
Safety Outcome Measures	• Incidence of device related and/or protocol procedure related adverse events related to the M•wrap study device

Study Success Criteria	**Primary Performance Goals:** • M•care FHR limit of agreement (LOA) within the performance goal of 15 beats per minute (bpm) of FHR measured with CTG. • M•care MHR limit of agreement (LOA) within the performance goal of 10 beats per minute (bpm) of MHR measured with CTG. **Secondary Performance Goal:** • M•care UC detection sensitivity with a performance goal of greater than or equal to 80% agreement.
Study Methodology	Subjects will be assessed for study suitability based on the stated inclusion and exclusion criteria. Once informed consent is obtained, the study monitoring systems will be applied to the subject's abdomen. Recording session: • Prior to deployment of the M•care system, subjects will be monitored with the external CTG device for fetal heart rate detection and the CTG pulse oximeter for maternal heart rate signal confirmation. • The M•wrap will be modified to allow positioning of the CTG transducers for simultaneous recording with both devices for FHR, MHR and UC (refer to Appendix 1). • The modified M•wrap will be secured to the subject's abdomen and the subject will be monitored in stationary position for the duration of study recording session while following the M•wrap Instructions for Use. • Data is transmitted from the M•care system application to the Marani Cloud. There, the Marani proprietary signal processing is performed, and the data are analyzed to identify clean MHR, FHR and UC signals. Comprehensive analysis of the values will be performed offline. Each recording session will last for a minimum of 60 minutes and no longer than 120 minutes. Following the completion of the session, the study staff will remove the M•care monitoring system from the maternal abdomen and the study session will be concluded. The equivalence of the M•care System data will be compared to that of the simultaneously obtained reference device data. Complete monitoring strips will be obtained for each device and monitoring session to allow comparison for determination of equivalence. Comparison assessments between the M•care and CTG device will evaluate FHR, MHR and UC. Blinded review of UC data will be conducted by two physicians experienced in obstetrics; in the event of discordance, a third blinded reviewer will serve as an adjudicator.

	At all times, the M•care system shall be considered a research device. In the clinical setting (i.e., not a research-only visit), the M•care system is an adjunct to routine care and not a replacement for routine or urgent care needs. Only the data from the standard of care reference devices will be available to the clinical care team. Data recorded by the M•care system will not be accessible by study team members, thus clinical decisions for all subjects will solely be based on standard of care practices.
Statistical Considerations	**Success Criteria:** Study success will be based on the following two primary performance goals: <u>Primary performance goal, FHR</u> The primary performance goal will be met if the 95% confidence interval for the 95% limits of agreement (LOAs) between the M•care System and the standard of care reference device for the primary performance endpoint, FHR are within the performance goal interval of [-15, 15] bpm. <u>Primary performance goal, MHR</u> The primary performance goal will be met if the 95% confidence interval for the 95% limits of agreement (LOAs) between the M•care System and the standard of care reference device for the primary performance endpoint, MHR are within the performance goal interval of [-10, 10] bpm. <u>Secondary performance goal, UC</u> The performance goal for the secondary endpoint, UC, will be met if the lower bound of the 2-sided 95% confidence interval for sensitivity is greater than 80% for M•care as compared to standard of care reference device. **Sample Size Justification:** A sample size of N=80 evaluable subjects with an average of 60 minutes of comparative device data will provide adequate power to establish equivalence between M•care and standard of care in the primary performance measurements of FHR and MHR, and the secondary performance measurement of UC event sensitivity. It is anticipated that up to 130 subjects from a minimum of 3 sites may be recruited to allow for inability of approximately 30% of subjects to complete the Monitoring Session per the study protocol. <u>Background</u> Mhajna et al reported the mean difference and (95% LOA) [SD] between INVU and standard of care reference CTG for FHR and MHR measurements as -0.30 bpm (-8.84, 8.24) [SD=4.36] and 0.28 (-5.30, 5.86) [SD=2.85], respectively.[1] Furthermore, Hayes-Gill et al[2] and Mhajna 2021[3,4] reported positive agreement (e.g., sensitivity) rates vs IUPC in uterine contraction events of 88%.

	Power Considerations In this study, each recording session will last for a minimum of 60 minutes and no longer than 120 minutes yielding an assumed minimum of 30 observations per subject for FHR and MHR, and an average of 3 UC events per subject. FHR and MHR are assumed to be normally distributed, with FHR mean (SD) of -0.3 (4.4), MHR mean (SD) of 0.3 (3). UC sensitivity is assumed to be distributed binary, with UC sensitivity of 90%. For all measurements, the within subject correlation is assumed to be 0.5 and compound symmetric. Based on these assumptions and simulations with SAS 9.4 statistical software of MMRM and bootstrap resampling analyses, N=80 evaluable subjects will provide greater than 80% power (using either statistical method MMRM or bootstrap resampling) to establish equivalence between M•care and standard of care in each of the primary performance measurements of FHR and MHR and UC event sensitivity according to the success criteria and performance goals described above.

1.2 SCHEMA

The subject visit flow is described in Figure 1 below.

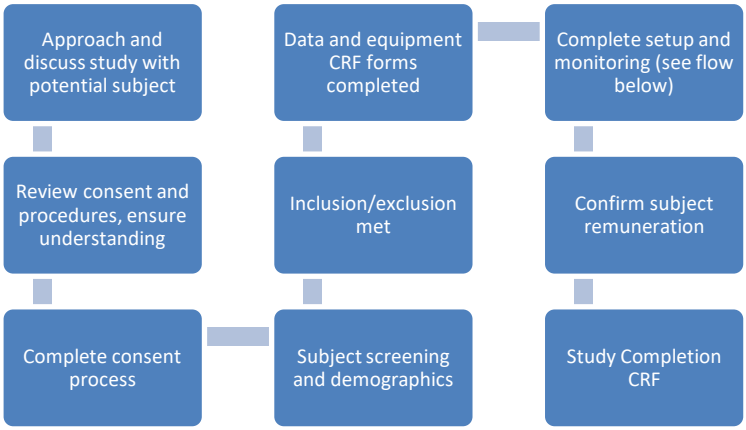

Figure 1. Subject Visit Flow

Once the Subject is present for data collection, the Setup and Monitoring Flow will proceed as shown in Figure 2. Throughout this protocol, the groupings are referred to as either "***Setup Flow***" or "***Monitoring Session***."

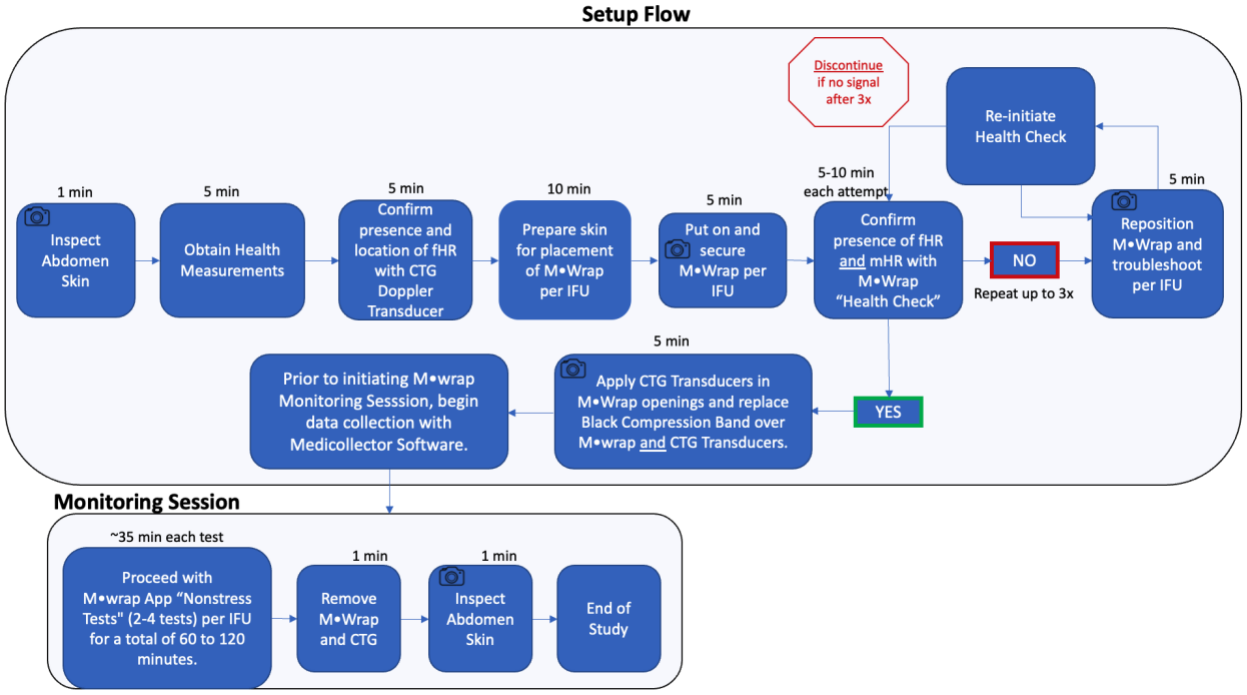

Figure 2. Setup and Monitoring Flow

2 INTRODUCTION

2.1 STUDY BACKGROUND

The U.S. has one of highest rates of maternal mortality in the industrialized world, putting the United States in the unenviable company of Afghanistan, Greece, and El Salvador.[5] Each year in the US, 700 to 900 women die from complications during pregnancy or childbirth. These numbers overshadow the more pervasive problem of severe maternal morbidity. Maternal health experts credit massive disparities in race, education, income, rural demographics, access to healthcare insurance and other socio-economic factors as prime reasons, accelerated by greater prevalence of C-sections, obesity, and chronic health issues including hypertension and diabetes. Pregnancy-related complications and premature births cost the US approximately $26B annually.

In the US there are substantial differences in maternal morbidity rates seen across racial and ethnic lines: non-Hispanic black women, Hispanic, Asian/Pacific Islander and American Indian/Alaska Native women were also significantly more likely to have a severe morbidity related to childbirth than white women.[6] Non-Hispanic black women have had the fastest rate of increase in maternal deaths between 2007 and 2014 and have maternal death rates up to 12 times higher in some cities than Non-Hispanic white women.[7–9] According to a recent publication containing data from 2018 from the National Center for Health Statistics, wide racial gaps exist between non-Hispanic Black (37.1 deaths per 100,000 live births), non-Hispanic white (14.7) and Hispanic (11.8) women.[10]

Monitoring systems used in labor and delivery are based on antiquated technology developed in the 1960s. These systems are bulky, and many technologies are still hardwired, technologically demanding, and plagued with inconsistent, inaccurate data output. The Marani M•care system utilizes novel, non-invasive sensors to leapfrog existing technology and provide inexpensive, easy-to-use garments that measure and record fetal electrocardiogram (fECG) along with other key biometrics.

Current clinical assessment of potential fetal distress during pregnancies is done through infrequent monitoring of the vital signs of mother and unborn child. Existing technologies, including doppler ultrasound, are used in clinical settings.

There are two types of monitoring-external and internal as standard of care:

External monitoring is generally performed intermittently during pregnancy to monitor fetal heart status for brief periods or to perform a non-stress test (NST) and is often used during labor and delivery. Short term external monitoring can be done by listening to the fetal heartbeat with a stethoscope or a handheld doppler. External monitoring is also frequently performed using Cardiotocography (CTG). With CTG, a doppler ultrasound sensor measures FHR and a second sensor measures contractions.

A non-stress test (NST) measures FHR in response to either fetal movement or uterine contraction (UC). The goal of the NST is to determine how the heart of a fetus responds to the stimulus of a UC or to its own movements. In a normal (reactive) NST, a fetal heart rate will increase in response to a UC or to fetal movement. At week 32 of pregnancy or later, if a baby's heartbeat accelerates to a certain level above the baseline twice or more for at least 15 seconds each within a 20-minute window, the results are considered reactive. If a baby's heartbeat does not meet the criteria described above, the results are considered nonreactive and further tests may be considered.

External FHR monitoring is also done for a contraction stress test (CST), which records changes of the fetal heart rate during uterine contractions (UC). The aim of this test is to monitor the fetus to check for heart rate abnormalities in response to UC using cardiotocography. CST antenatal fetal surveillance technique may help predict the fetal capability to tolerate the stress of labor and vaginal delivery.

Invasive internal monitoring using fetal scalp electrodes (FSE) and intrauterine pressure catheters (IUPC) are commonly used for intrapartum monitoring and management. These invasive technologies have known side effects including infection, particularly if the mother has an existing infection. In addition, use of these technologies requires that the amniotic sac be ruptured, and the mother's cervix be dilated to at least 2 cm. As such, these technologies are not generally available in the early stages of labor as standard of care.

2.2 STUDY RATIONALE

Marani is developing a proprietary, wearable sensor platform technology to non-invasively acquire maternal and fetal biometric data, including fetal ECG (fECG). The Marani Health M•care System will allow clinicians to assess fetal heart rate non-invasively and wirelessly for prenatal monitoring.

The Marani Health M•care System measures indicators of fetal and maternal wellbeing including fetal movements, maternal and fetal cardiovascular activity, and uterine contractions. The wearable system will simultaneously record both fetal and maternal parameters non-invasively. The Marani M•care product provides robust FHR, MHR and UC measurements compared to the standard of care CTG monitoring devices.

2.3 BENEFIT/RISK ASSESSMENT

This is a minimal risk study. The subjects in this study are not expected to be at any higher or additional risks than those who undergo cardiotocography (CTG) monitoring in clinic or hospital settings. There is minimal risk with CTG monitoring.

The M•wrap device employs electrocardiograph electrode sensors that are Food and Drug Administration (FDA) cleared. An electrocardiograph electrode is an electrode applied directly to the subject's skin to passively acquire and transmit the electrical signal at the body surface to a processor that produces an electrocardiogram (ECG) or vectorcardiogram. An electrocardiograph electrode is not intended to deliver

therapy to the subject, and information collected from the subject using the M•wrap will not be used to provide any treatment or treatment recommendations during the study. There is no personal benefit to the subject for taking part in this study. Subject benefit is limited to the understanding that they are contributing to research on a new device that may benefit others in the future.

The M•wrap is worn like tight-fitting compression clothing. Some people may view this as mildly uncomfortable. In addition, pressure artifacts on the abdomen or back are expected. Anticipated risks of the M•wrap system include but are not limited to known events associated with the use of ECG electrode systems and compression garments.

- Redness (erythema)
- Swelling (edema)
- Irritation
- Sensitization

Skin irritation will be carefully monitored before, during, and after the study session. Subjects will be immediately evaluated by the site investigator for any relevant unexpected skin irritation. Marani has designed the M•wrap to meet all applicable performance standards.

Privacy Protection: Acquired data from this study will be stored on HIPAA-compliant, encrypted servers. Only investigators, engineers, statisticians, and other study personnel involved in data recording and interpretation will be allowed access to these data.

3 OBJECTIVES AND ENDPOINTS

3.1 OBJECTIVE

The objective of this study is to demonstrate the safety and performance of the Marani Fetal Monitoring Telehealth System (M•care™ System) for use in antenatal monitoring of pregnant women ≥ 32 weeks' gestation. The M•care System will be evaluated by comparing Fetal Heart Rate (FHR), Maternal Heart Rate (MHR) and Uterine Contractions (UC) to Doppler FHR, Pulse Oximeter MHR, and tocodynamometer (TOCO) UC, respectively, measured with an FDA cleared standard of care cardiotocography (CTG) device.

3.2 PRIMARY PERFORMANCE MEASURES

1) M•wrap FHR limit of agreement (LOA) within the performance goal of 15 beats per minute (bpm) of FHR measured with CTG
2) M•care MHR limit of agreement (LOA) within the performance goal of 10 beats per minute (bpm) of MHR measured with CTG

3.3 SECONDARY PERFORMANCE MEASURES

The secondary performance measure is Uterine Contractions (UC) sensitivity as measured by the M•care System versus the standard of care CTG device, with a performance goal of greater than or equal to 80% agreement. Sensitivity is defined as the proportion of UC events identified by standard of care that are simultaneously (e.g., within 30 seconds) identified by the M•care System.

Hypothesis testing for UC sensitivity will only be conducted if the primary performance measures (i.e., equivalence in FHR and MHR) are met.

Additional UC endpoints as measured by the M•care System verses standard of care CTG device include:

1) Positive predictive value (PPV) defined as the proportion of UC events identified by both the M•care System and standard of care out of those that are identified by the M•care System
2) False Positive Rate defined as the proportion of UC events identified by the M•care System that are not identified by the standard of care

No hypothesis testing is planned for the PPV and false positive rate endpoints.

3.4 SAFETY ENDPOINT MEASURES

Incidence of device related and/or protocol procedure related adverse events (AEs) related to the study device, The Marani Health M•care System, in pregnant women with a singleton pregnancy ≥32 gestational weeks. Due to minimal risk, we do not expect any related serious events (see safety in section 8).

3.5 SUCCESS CRITERIA JUSTIFICATION

Fetal Heart Rate (FHR)

The primary performance endpoint is M•care FHR limit of agreement (LOA) within 15 beats per minute (bpm) of FHR measured with cardiotocography. This 15 bpm LOA is a clinically acceptable range to recognize common clinical phenomena including bradycardia, tachycardia, accelerations, and decelerations.[7] Most FHR clinical phenomena are defined as an increase or decrease of 15 bpm from baseline, which could be detected given a 15-bpm limit of agreement. Clinical practice guidelines state that moderate FHR variability, between 5 and 25 bpm, is considered normal.[11] Baseline HR variability can range from 3-12 bpm as measured with standard CTG, and which increases with gestational age.[7,12] Moreover, FHR calculations derived from CTG have previously been shown to have a high degree of inaccuracy when compared with those derived from fetal ECG-based measurements.[7] Thus, given the known limitations of CTG, some of variability quantified by the limits of agreement in this study may be due to error in CTG measurements and not M•wrap measurements.

In a study reported by Cohen, et al, the limits of agreement for both FHR and MHR with FSE, abdominal fetal ECG and ultrasound were clinically evaluated.[13] In this study, the abdominal fetal ECG limits of

agreement (± 1.96 SD) for fECG to FSE was 8.40; −8.72 and for the Doppler ultrasound technique the bias is significantly greater, −2.87, with limits of agreement of (22.65, −28.39)[7] indicating an even wider interval may be considered clinically insignificant. The FHR performance goal interval of [-15, 15] bpm is based on the clinically significant margin for differences in FHR that have been variously reported in the literature as: >15bpm (e.g., large acceleration)[14], and >25bpm (e.g., marked baseline variability).[15]

The mean difference (bias) between FHR measurements with fECG and Doppler methods has been reported as 0.74 bpm with 95% LOA of +/- 12 bpm (e.g., SD= 6.1 bpm) by Reinhard et al[14], and -0.3 bpm with 95% LOA of (-8.84, 8.24) (e.g., SD=4.36) by Mhajna et al.[1] The Monica Health Novii wireless patch system Instructions for Use (107-PT-005-EN rev P) indicates that when comparing the Monica Novii System and the predicate Monica AN24 System, the 95% LOA was -13.7BPM to 14.1 BPM.

Maternal Heart Rate (MHR)

The primary performance endpoint is M•care MHR limit of agreement within 10 beats per minute (bpm) of MHR measured with Pulse Oximetry MHR with the CTG. It has been shown that a woman's heart rate increases by an average 10 to 20 bpm during pregnancy.[16] The mean heart rate at 34-42 weeks' gestation was reported by Van Oppen et. Al as 92 ± 1.[17] Sherman, et. al showed that heart rate variability is 15.8 ± 1.8 during the latent phase and 12.7 ± 1.1 during the active phase of the first stages of labor.[18] Other clinical studies have chosen an increase or decrease in heart rate of ≥10 beats per minute (bpm) at the peak of a contraction as compared to 10 seconds before the contraction to be regarded as either an acceleration or deceleration.[19] As such, these reports support that a 10 bpm LOA is a clinically acceptable range to recognize common clinical phenomena including accelerations and decelerations. Additional considerations for tachycardia and bradycardia have been considered. Odendaal et al. reported that tachycardia is defined as a "rate of at least 100 beats per minute under resting conditions" while the definition of bradycardia in pregnancy "has not been standardized."[20]

Uterine Contractions

Uterine contractions are identified based on the tracings output by the relevant device; knowledgeable readers interpret the tracings to identify the contractions. The outcomes are binary: either the event happened, or it did not. To evaluate the performance of this binary outcome, our success criterion is to obtain results consistent with cleared devices with similar technologies such as the Monica AN24 per K101801 510(k) Summary, Monica Novii Instructions for Use (107-PT-005-EN rev P), and TOCO[13] in general.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Hypothesis: We hypothesize that non-invasive electrical recordings will permit acquisition of the fetal ECG, maternal ECG and uterine contractions (UC) with proper signal processing and will ultimately support the development of an abdominal fetal monitor that is wireless and unobtrusive. This will be accomplished with the Marani M•wrap wearable garment.

This study is a prospective paired comparison, multi-site trial intended to establish the equivalence of the Marani M•care System with FDA-cleared Doppler FHR, TOCO UC and pulse Ox MHR reference. Subjects who are admitted to triage for potential labor or other inpatient evaluations including but not limited to evaluation for PROM, who are attending in-clinic appointments for Non-Stress Tests (NST), Contraction Stress Test (CST), or at the convenience of the subject will be monitored with both devices simultaneously for FHR, UC, and MHR. Only the data from the CTG device, the standard of care, will be available to the clinical team in a clinical setting. CTG information will not be interpreted in a non-clinic research visit setting. The M•care System data will be compared to that of the simultaneously obtained standard of care CTG data to determine equivalence after the monitoring is completed. No interim analysis is planned.

4.2 END OF STUDY DEFINITION

Subjects will complete this study Setup and Monitoring sessions in a single visit. Consenting and Screening may occur at a different time prior to Setup. Each individual subject study will be considered complete when **all** the following conditions have been met:

- Consenting process has been completed
- M•wrap monitoring is complete for that subject
- Transmission of subject data has been confirmed by Marani, and
- All study CRFs are finished.

The overall study will be considered complete when **all** the following conditions have been met:

- All subjects have completed their study visits as described above
- Data queries have been adjudicated
- Database is closed, and
- All sites have had their closeout monitoring visits and received their closeout confirmation letter.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Subjects eligible for this clinical study must fulfill **all** the following criteria:

1) Able to provide Informed Consent and follow study instructions
2) 18 years of age or older
3) Pregnant subjects ≥ 32 weeks' gestation
4) Singleton pregnancy
5) BMI ≥15, pre-pregnancy
6) BMI ≤45, pre-pregnancy
7) Belly circumference ≥80 cm and ≤ 135 cm

NOTE: Subjects admitted for induction of labor and subjects being monitored for premature rupture of membranes (PROM) or other inpatient evaluations can be enrolled in the trial.

5.2 EXCLUSION CRITERIA

Subjects are not eligible if **any** of the following criterion are met:

1) Known major fetal malformation or chromosome abnormality
2) Abdominal medical skin conditions, including surgical incisions, open wounds with or without infections, edema, or irritation
3) Subjects with implanted electronic devices (pacemakers, defibrillator, etc.)
4) Involvement in another clinical trial currently or previously in this pregnancy that, in the investigator's opinion, would affect the conduct of this study.
5) Medical or obstetric problem that in investigator's opinion would make the subject incapable of taking part in the study.
6) In the investigator's opinion, the subject is not likely to be available for the minimum 60 minutes of the monitoring session.
7) History of skin allergies to cosmetics and lotions.
8) Known allergies to silver, nylon, or polyester.

   Note: some people with sensitivity to silver jewelry are sensitive to the impurities in silver alloys and not to silver itself.

5.3 SCREEN FAILURES

Consented screen failures are defined as subjects who consent to participate in the clinical trial but are not entered into the study due to unmet inclusion or exclusion criteria. A screen failure log will be maintained at each site.

5.4 STRATEGIES FOR RECRUITMENT

Recruitment will include pregnant women (≥32 weeks) who are coming to clinic for routine antenatal visits, scheduled research visits, or who are presenting for scheduled induction of labor, admitted for premature rupture of membranes (PROM) or other inpatient evaluations, in observation in labor triage. Visits will be scheduled at the convenience of the mother.

The study will enroll a minimum of 80 evaluable subjects. Two study groups will be included in order to ensure collection of sufficient uterine contraction activity data. The study groups are as follows:

- Antenatal – includes subjects evaluated per obstetric standard of care in the clinic/office environment and subjects completing research-only visits in a non-clinic setting with oversight by a healthcare professional. Subjects with premature rupture of membrane (PROM) will also be included.
- Enriched Hospital – includes subjects in early (latent) phase of labor with suspected or confirmed uterine contractions, subjects who are being induced for labor.

6 STUDY REGIMEN

6.1 STUDY ADMINISTRATION

The group of subjects enrolled into the study may include subjects scheduled for routine antenatal visits; participation in the study may be offered while in the office for their scheduled visit. Other eligible subjects may be recruited from the general population for a scheduled research visit in a non-clinical setting. Each subject may identify a time that works best for them. During the visit (subjects must be 32 weeks or greater), fECG, mECG signals and UC will be recorded. The aim is to record signals for up to 120 min. The definition of success is: (1) capture of signals with CTG and (2) validation that the M•wrap is capturing signals.

The sequential order for recording, based on our estimation of the likelihood of success, is as follows:

1. Apply the CTG doppler transducer and confirm the CTG doppler transducer is operating normally. Remove the doppler transducer and put on M•wrap.
2. Utilize M•wrap + CTG (FHR, MHR, and UC) to collect data.

For purposes of recording signals, data will be collected from the subject simultaneously using both the M•wrap and CTG. Refer to Section 1.2 for the expected step-by-step Study Schema. The FHR will be located with the doppler transducer on the CTG. Once a strong FHR is located, prepare for and conduct placement of the appropriately sized M•wrap placement per the current Instructions for Use (IFU) Manual. With guidance from Marani, holes/openings will be created in the wrap fabric to allow for placement of the CTG transducers such that both devices can be used simultaneously. See Figure 3 for an example of wrap placement and use of the wrap with CTG transducers. Appendix 1 describes M•wrap configurations for concurrent CTG use in more detail. The black compression band will be placed over the M•wrap and the CTG transducers throughout simultaneous data collection (see Figure 4). Marani personnel will be present to perform necessary device modifications to allow for CTG placement and to initiate data collection from the M•care Mobile Application.

Based on the design of the M•care Mobile Application, each 60-to-120-minute Monitoring Session may include up to four data collection initiations from the M•care Mobile Application. The mother may get up and walk around between data collection sessions.

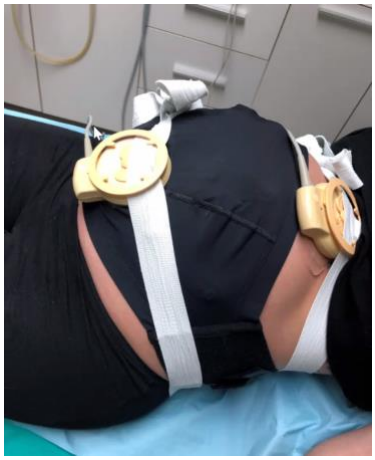

Figure 3. M•wrap with Example CTG Placement

Figure 4. Black Compression Band over M•wrap and CTG Transducers

Uterine contractions will be recorded using the standard external acquisition tocodynamometer system within the CTG, and the information synchronized to the recorded biopotential signals. These signals will be collected over a 60-120 min period.

Figure 5 depicts the connectivity of the Marani M•care System. The M•wrap signal will stream via Bluetooth through the M•core to a Marani-provided mobile phone containing either Android or iOS operating system and then to a secure Marani server (utilizing Amazon Web Services). The CTG signals labeled only with Subject ID will be extracted from a MIB / RS232 port on the CTG machine and captured on a Marani-provided laptop for analysis and comparison to the M•wrap data. A Medicollector Cable CBL-5010 will be used to connect the CTG to the Marani-provided laptop. For the purpose of this study, the

subject-facing mobile application will be controlled by Marani. Site specific procedures will be followed for information security.

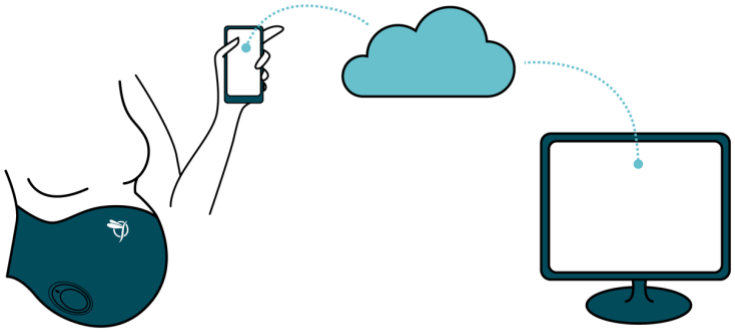

Figure 5. Marani M•care System

Study subjects may be asked to be photographed to demonstrate where the electrodes are meeting the subject's abdomen, and possibly for publication. Photographs will only include abdominal pictures of the M•wrap; no identifying photos of faces will be included.

Study garments and cores will be reused across subjects. Cleaning procedures to allow for reuse of garments are in accordance with FDA and CDC guidelines for non-critical subject care items. Applicable references include FDA's 2015 Guidance "*Reprocessing Medical Device in Health Care Settings; Validation Methods and Labeling*" and CDC's 2008 Guideline document, "*Guideline for Disinfection and Sterilization in Healthcare Facilities*."

6.2 ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

An adequate number of M•wrap and M•core devices will be supplied to each study site prior to initiating the study and may be resupplied as needed. Each shipment of device supplies for the study will contain a shipment form to assist in maintaining current and accurate inventory records. When a device shipment is received, the investigator/coordinator will acknowledge receipt.

Accountability records will be maintained at the site at all times. The identification number of the subject, the date, lot number, expiration date of the M•wrap dispensed, and the date and quantity of devices returned will be recorded. The devices will be noted on the appropriate inventory forms. Per Marani Health or Marani Health designee visit at the site, accountability of the returned devices should be performed and recorded.

Upon conclusion of the study, all devices must be returned to the sponsor or the sponsor's designee. Ancillary supplies (i.e., CTG bands, isopropyl alcohol, mild detergent, ultrasound gel for CTG transducers) may not need to be returned.

6.2.2 APPEARANCE AND LABELING

The devices provided for this study will be labeled as investigational use only. Unique identifiers will be recorded to enable tracking of necessary device elements. Software versions used in the clinical study will be recorded.

7 STUDY DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF M•WRAP APPLICATION/SUBJECT WITHDRAWAL

Subjects may withdraw from the study at any time. In the event that a subject experiences any adverse events, the protocol may be stopped, and the investigators will analyze the root cause. In addition, fetal wellbeing will be monitored and, if there are any effects considered to be the result of the study, the study may be stopped and there will be routine management of any subject if being seen in a clinical setting. If the subject is being seen in a non-clinic research setting, no CTG data will be interpreted and any adverse events requiring medical attention will be referred to the subject's physician. All adverse events will be followed with relevant records requested until resolution whenever possible. Each site investigator in a clinical setting will be responsible for determining appropriate clinical care. Site clinical staff may also make the decision to withdraw a subject for any other reason.

The reason for withdrawal/discontinuation should be recorded on the appropriate case report form (CRF). Data collected up to the point of withdrawal may be used.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

In order to assess efficacy, data will be collected simultaneously with both the M•wrap and CTG; this allows for a direct comparison of data obtained. CTG is considered standard of care and only that information will be used for clinical interpretation if the research is carried out in a clinical setting. The M•wrap data will not be shared with the practitioner or the subject and will not be used for any clinical interpretation or interventions. In the event the M•wrap location and position prevents CTG data acquisition necessary for care, the M•wrap will be removed, replaced, or repositioned. The study session will be stopped if standard of care cannot be achieved with the M•wrap in place.

8.2 SAFETY AND OTHER ASSESSMENTS

During the time any subject is wearing the M•wrap, safety will be monitored. In the clinical setting, a qualified site staff member designated as having appropriate clinical expertise will make determinations regarding appropriate clinical care and care will be provided for any adverse events. If adverse events occur in the non-clinical setting, subjects will be referred to a clinician for treatment as needed.

In the clinical setting, monitoring for fetal wellbeing with standard of care shall be continued. If the subject is being seen in a research visit setting, no interpretations will be made from CTG or the M•wrap.

8.3 ADVERSE EVENTS

8.3.1 ADVERSE EVENTS (AE)

Refer to section 10.6 for a list of adverse event terms and definitions.

Adverse events (AEs) will be monitored throughout the study period. All adverse events that occur during the time a subject is wearing the M•wrap will be collected and reported to Marani according to section 8.3.2. Potential AEs for this study are listed in the 'Benefit/Risk Assessment' in Section 2.3. Events or complications unrelated to the M•wrap system will not be collected after removal of the M•wrap device.

Since the study procedures are not greater than minimal risk, Serious Adverse Events (SAEs) are not expected. If any problems related to subjects do occur, these will be reported to the Institutional Review Board (IRB) in accordance with the local institution's applicable policies and procedures.

8.3.2 REPORTING OF AN ADVERSE EVENT

All AEs and device deficiencies should be reported to Marani Health on the appropriate CRF within 24 hours of awareness. Marani Health will be responsible for device servicing and replacements.

AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB per local IRB reporting requirements.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

Adverse events will be classified by seriousness, severity, and relationship to study device and protocol procedures. Marani Health will be responsible for device servicing and replacements.

For adverse events, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the subject's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.1 RELATIONSHIP TO STUDY APPLICATION

All adverse events will have their relationship to study application and protocol procedures assessed by the study staff who examines and evaluates the subject based on temporal relationship. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study application administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study application (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study application, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study application). However, other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study application administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study application) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study application administration, and/or evidence exists indicating that the event is definitely related to another etiology. An alternative, definitive etiology must be documented by the study staff.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, study staff's assessment of severity, relationship to study product and protocol procedures, and time of resolution/stabilization of the event. All AEs will be followed to adequate resolution.

8.3.5 EXPEDITED REPORTING REQUIREMENTS

An investigator shall submit to the sponsor and to the reviewing IRB a written report of any unanticipated adverse device effect (UADE) occurring during an investigation according to the IRB's applicable policies and procedures, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)).

9 STATISTICAL CONSIDERATIONS

9.1 ANALYSIS POPULATIONS

For all analysis populations the Hospital and Antenatal groups will be combined. Additional supportive analyses will be conducted for each study group separately.

The safety analyses will be conducted for the Safety Population defined as the population of subjects who enter the setup process (see Section 1.2, Schema) regardless of evaluability for performance measures.

The Performance Evaluable Population will be the primary analysis population for performance measures and will be defined as the population of subjects who:

- Enter the monitoring phase per Section 1.2, Schema;
- Have at least 1 minute of concurrent data with both devices; and
- Do not have any major protocol violations.

9.2 STUDY ENDPOINTS

9.2.1 PRIMARY PERFORMANCE MEASURES

- Fetal Heart Rate (FHR) as measured by the M•care System versus standard of care CTG device.
- Maternal Heart Rate (MHR) as measured by the M•care System versus the standard of care CTG Pulse Ox.

9.2.2 SECONDARY PERFORMANCE MEASURES

The secondary performance measure is Uterine Contractions (UC) sensitivity as measured by the M•care System versus the standard of care CTG device. Sensitivity is defined as the proportion of UC events identified by standard of care that are simultaneously (e.g., within 30 seconds) identified by the M•care System.

Hypothesis testing for UC sensitivity will only be conducted if the primary performance measures (i.e., equivalence in FHR and MHR) are met.

Additional UC endpoints as measured by the M•care System versus standard of care CTG device, include:

- Positive predictive value (PPV) defined as the proportion of UC events identified by both the M•care System and standard of care out of those that are identified by the M•care System.
- False Positive Rate defined as the proportion of UC events identified by the M•care System that are not identified by the standard of care.

No hypothesis is planned for the PPV and false positive rate endpoints.

9.2.3 SAFETY OUTCOME MEASURES

Incidence of device related and/or protocol procedure related adverse events (AEs) related to the M•wrap study device.

9.3 STUDY SUCCESS CRITERIA

9.3.1 PRIMARY PERFORMANCE GOALS

Study success will be based on the following:

- M•care System limit of agreement (LOA) as compared with CTG within the performance goal of 15 beats per minute (bpm) for FHR.
- M•care System limit of agreement (LOA) as compared with CTG within the performance goal of 10 beats per minute (bpm) for MHR.

9.3.2 SECONDARY PERFORMANCE GOAL

- M•care System UC detection sensitivity with a performance goal of greater than or equal to 80% agreement with CTG.

9.4 STATISTICAL ANALYSIS

9.4.1 GENERAL CONSIDERATIONS

Each recording session will last for a minimum of 60 minutes and no longer than 120 minutes with multiple observations per subject for FHR and MHR and UC events. For analysis of UC events, blinded review will be conducted by two physicians experienced in obstetrics. In the event of discordance, a third blinded reviewer will serve as an adjudicator.

Descriptive statistics will include n, mean, median, standard deviation, minimum and maximum for continuous data and n and percentages for categorical data. To account for the correlation among multiple measurements within subjects, MMRM (mixed-effect model repeated measures) statistical methods will be utilized for the primary analyses, with bootstrap resampling methods conducted as a supportive analysis. Unless otherwise specified all statistical tests will be conducted at a 2-sided alpha of 5%.

9.4.2 SUBJECT ACCOUNTABILITY, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

For each analysis population, the number of subjects will be summarized for each accountability status (e.g., consented, screen failed, enrolled, completed study, or withdrawn). Subjects excluded from an analysis population will be provided in a listing including reason for exclusion (e.g., non-evaluable for performance measures, major protocol deviation, etc.).

For this study, enrollment is defined as subjects who enter the Setup phase per Section 1.2, Schema. Subjects who do not meet these minimum criteria will not be considered enrolled and will not be included in any analysis of performance for safety measures.

Demographic characteristics (age, sex, race, ethnicity, height, weight, pre pregnancy BMI) will be summarized using descriptive statistics for each analysis population.

Baseline obstetrical characteristics will be summarized using descriptive statistics for each analysis population, including obstetrical history, appointment or admission type, and belly circumference.

9.4.3 PERFORMANCE MEASURES ANALYSES

Primary Performance Measures Analysis

A comparison between M•care measurement of FHR vs the standard of care reference measurements will be made using methods described below to test the following equivalence hypothesis corresponding to the Success Criteria defined in Section 3.5 of this protocol:

H0: Upper 95% LOA > 15 bpm or Lower 95% LOA < -15 bpm vs

H1: -15 bpm ≤ Lower 95% LOA and Upper 95% LOA ≤ 15 bpm

A Bland-Altman plot of the mean versus the difference will be presented, and the 95% limits of agreement (LOA) calculated together with respective 95% confidence intervals, which will be compared to the equivalence threshold (e.g., performance goal). Both MMRM analysis (primary) as well as bootstrap resampling techniques (supportive) will be conducted to account for the correlation among repeated FHR measurements within subjects. For the MMRM analysis, the mean difference (bias) and its standard deviation will be estimated from the intercept of the model, assuming a compound symmetric correlation

structure, with the 95% LOA and corresponding 95% confidence intervals calculated as defined by Lu 2016.[21] MMRM analysis provides for valid inference in the presence of data that is missing at random.

In addition, a Deming regression model will be fitted to the FHR values obtained from both devices; the slope (β1) and intercept β0) together with respective 95% confidence intervals will be presented. The confidence intervals of the regression parameters will be calculated with bootstrap resampling methodology, to accommodate repeated measurement within subjects. The results will be presented graphically via scatter plot with the line of slope 1 and intercept 0 superimposed.

A comparison between M•care measurement of MHR vs the standard of care reference measurements will be made using the methods described above to test the following equivalence hypothesis Success Criteria defined in Section 3.5 of this protocol:

H0: Upper 95% LOA > 10 bpm or Lower 95% LOA < -10 bpm vs

H1: -10 bpm ≤ Lower 95% LOA and Upper 95% LOA ≤ 10 bpm

Secondary Performance Measures Analysis

A comparison of sensitivity in UC events detected with M•care measurement vs the standard of care will be made using methods described below to test the following hypothesis:

H0: Sensitivity < 80% vs H1: Sensitivity ≥ 80%

To compare sensitivity (percent positive agreement) in UC events between M•care and standard of care, both MMRM analysis for binary data (primary) and bootstrap resampling techniques (supportive) will be used to account for the correlation among repeated UC measurements within subjects. For the MMRM model, the sensitivity will be estimated from the intercept of the model, presented with corresponding 2-sided 95% confidence interval (e.g., corresponding to a 1-sided alpha 2.5%).

Estimates of false positive rate and PPV in UC events detected with M•care measurement vs the standard of care will be made using both MMRM analysis for binary data (primary) and bootstrap resampling techniques (supportive), to account for the correlation among repeated UC measurements within subjects. For the MMRM model, estimates will be from the intercept of the model, presented with corresponding 2-sided 95% confidence interval.

Primary and secondary performance measures will also be summarized using descriptive statistics for FHR and MHR, and using a 2x2 cross tabulation table for UC events.

9.4.4 SAFETY MEASURES ANALYSIS

The incidence and overall counts and classifications of adverse events that are related to the M•wrap study device and/or protocol procedure will be summarized for the safety population. Summaries will

include incidence and counts overall for AEs and SAEs, by category, severity and by relationship to study device and /or protocol procedure.

9.4.5 ADDITIONAL ANALYSES AND CONSIDERATIONS

The following analyses will be conducted as supportive analyses to the primary analyses described in Section 9.4.3:

Subgroup Analyses

Primary performance measures will be presented separately by the following subgroups and evaluated for consistency:

- BMI strata (Low ≤ 29; Medium > 29 and ≤ 35; High > 35 and ≤ 45)
- Race
- Study group (Antenatal and Enriched Hospital), defined as follows:
    - Antenatal – includes subjects evaluated per obstetric standard of care in the clinic/office environment and subjects completing research-only visits in a non-clinic setting with oversight by a healthcare professional. Subjects with premature rupture of membrane (PROM) will also be included.
    - Enriched Hospital – includes subjects in early (latent) phase of labor with suspected or confirmed uterine contractions, and subjects who are being induced for labor.

Primary performance measures data will be analyzed for all subjects regardless of major protocol deviations, where available.

Missing Data and Invalid Data

Only valid synchronized data will be analyzed. Missing performance measurement data will not be imputed. Determination of invalid signals will be addressed by data management according to written work instructions.

9.5 SAMPLE SIZE JUSTIFICATION

A sample size of N=80 evaluable subjects with an average of 60 minutes of comparative device data will provide adequate power to establish equivalence between M•care and standard of care in the primary performance measurements of FHR and MHR, and the secondary performance measurement of UC event sensitivity according to the success criteria and performance goals presented in Statistical Considerations Section 9.3. It is anticipated that up to 130 subjects may be recruited to allow for inability of approximately 30% of subjects to enter the Monitoring Session phase of the study.

Background

Mhajna et al reported the mean difference and (95% LOA) [SD] between INVU and standard of care reference CTG for FHR and MHR measurements as -0.30 bpm (-8.84, 8.24) [SD=4.36] and 0.28 (-5.30, 5.86) [SD=2.85], respectively.[1] Furthermore, Hayes-Gill et al[2] and Mhajna et al[3,4] reported positive agreement (e.g., sensitivity) rates vs IUPC in uterine contraction events of 88%.

Power Considerations

In this study, each recording session will last for a minimum of 60 minutes and no longer than 120 minutes yielding an assumed minimum of 30 observations per subject for FHR and MHR, and an average of 3 UC events per subject. FHR and MHR are assumed to be normally distributed, with FHR mean (SD) of -0.3 (4.4), MHR mean (SD) of 0.3 (3). UC sensitivity is assumed to be distributed binary, with UC sensitivity of 90%. For all measurements, the within subject correlation is assumed to be 0.5 and compound symmetric.

Based on these assumptions and simulations with SAS 9.4 statistical software of MMRM and bootstrap resampling analyses as described above in Statistical Considerations Section 9.4, N=80 evaluable subjects will provide greater than 80% power (using either statistical method MMRM or bootstrap resampling) to establish equivalence between M•care and standard of care in each of the primary performance measurements of FHR and MHR and UC event sensitivity according to the success criteria and performance goals presented in Statistical Considerations Section 9.3.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to each individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and each subject will be asked to read and review the entire document. The trained study staff will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will

be given to the subjects for their records. The informed consent process will be conducted and documented in accordance with standard processes before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The consenting process may be done remotely depending on site-specific regulations and capabilities. If remote consenting is employed, all required aspects of the consenting process must be documented and meet HIPAA privacy regulations.

After identifying a subject who meets minimum eligibility criteria before collecting study data, the study will be explained in detail to the subject including: (1) that the study represents a research effort, (2) that participation is voluntary, and there is no penalty for withdrawal, (3) potential risks and benefits of participation, (4) the procedures to ensure privacy of their medical information, and (5) contact information for addressing additional concerns. Subjects are informed of the purpose of the study and of their options to accept or refuse entry into the study. Only with the full and complete understanding of the study, and signed informed consent, will the evaluation of the potential subject continue. In accordance with 21 CFR parts 50 and 56, all subjects must provide written informed consent in accordance with each clinical site's Institutional Review Board/Medical Ethics Committee (IRB/MEC). A copy of the consent form from each center must be forwarded to Marani Health. Approvals for continuation of the study at each clinical site must be obtained according to their local IRB/MEC requirements (at a minimum, annually).

Foreign language consenting may be approved at the site per local rules.

Subjects will receive remuneration following completion of study activities as set forth by the reviewing Institutional Review Boards (IRB).

10.2 ETHICAL CONSIDERATIONS

The investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki, and with the regulations and guidelines of the FDA (all state/local regulations) and ISO 14155, whichever affords greater protection to the subjects.

10.3 INSTITUTIONAL REVIEW BOARD (IRB)

The study must have unconditional IRB approval in writing; language should be approved by local site IRBs. A copy of the Letter of Approval from the local IRB, which contains specific identification of the documents approved, must be received by Marani Health prior to site initiation.

Any amendments to the protocol or subsequent changes to the informed consent form as a result of changes to the protocol and/or IFU approved by Marani Health must also be approved, as appropriate, by the IRB and documentation of this approval provided to Marani Health. Records of the IRB review and

approval of all documents pertaining to this study must be kept on file at the site by the investigator and are subject to regulatory authority and/or sponsor inspection during or after completion of the study.

Continuing Review reports must be submitted to the IRB as required, as well as notification of completion of the study and a final report where applicable. A copy of all reports submitted to the IRB must be sent to the sponsor.

10.4 PROTOCOL AMENDMENTS

Major changes to the protocol should only be made by an approved protocol amendment. Protocol amendments must be approved by the Sponsor and each respective site's IRB prior to implementation.

10.4.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study subjects, investigator, sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform active study subjects, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoints have been met
- Determination of futility

If suspended, the study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or FDA requirements.

10.4.2 CONFIDENTIALITY AND PRIVACY

Confidentiality will be ensured at the site and by the sponsor throughout the study. All subject data will be identified only by a subject identification number. A key will be kept at each study site connecting subject identification numbers to names/demographic information in a secure location; this key will not be sent to the sponsor but may be monitored at the site. After obtaining each subject's consent, the investigator will permit the study monitor, independent auditor or regulatory agency personnel to review that portion of the subject's medical record that is directly related to the study. No other medical identifying information or PHI will be collected.

10.4.3 FUTURE USE OF DATA

After the study is completed, the de-identified, archived data will be stored electronically for future use by Marani. Permission to store data will be included in the informed consent.

During the conduct of the study, an individual subject can choose to withdraw consent to have data used for future research.

10.4.4 CLINICAL MONITORING

Marani will conduct monitoring at participating clinical sites to ensure that all Investigators comply with the protocol and the signed Investigator's Agreement. Sites will be required to report any circumstances in which an Investigator deviates from the clinical protocol; corrective action will be taken as necessary. Monitoring will be completed per the monitoring plan and may include remote monitoring as the site allows. Complete study documentation will be maintained at each site for records verification. The coordinator and/or investigator should be available to answer questions or resolve data clarifications.

Regulatory binder contents will also be monitored for completeness.

10.4.5 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks of the database will be generated. The web-based integrated system monitors and tracks data quality, including missing information, forms and any data lag for entry (i.e., overdue forms). In addition, the system reports the status of data quality both to the local center (at both a summary- and a subject-level report) and to Marani.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, Clinical investigation of medical devices for human subjects – Good Clinical Practice (ISO 14155:2020 GCP), and applicable regulatory requirements.

Each investigational site will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.4.6 DATA HANDLING AND RECORD KEEPING

10.4.6.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets (CRFs) will be provided for use as source document worksheets for recording data for each subject enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

10.4.6.2 STUDY RECORDS RETENTION

The investigator will maintain a comprehensive and centralized filing system of all relevant documentation in accordance with current standards and local rules. Investigators will be instructed to retain all study records required by Marani Health and regulatory authorities in a secure and safe facility with limited access for one of the following time periods based on notification from Marani Health:

- A period of at least three years from last marketing authorization and notification from sponsor; or
- A period of at least three years after discontinuation of clinical development of the investigational product as confirmed by Marani Health; or
- Longer, if required by local regulations

The investigator will request and receive written permission from Marani Health before disposal of any study records. Sites will provide written notification to Marani Health of any change in the location, disposition, or custody of the study files.

All files must be disposed of according to local and federal rules.

10.4.7 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol (ISO 14155:2020 GCP). The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report major deviations as defined by site reporting procedures. All deviations must be addressed in study source documents and reported to Marani on the appropriate CRF. Protocol deviations must be sent to the

reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements and policies.

10.4.8 TRIAL REGISTRATION

This trial will be registered with ClinicalTrials.gov. Study progress and results will be posted there as required.

10.4.9 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial and per the IRB. Potential conflicts are reviewed per local site guidance and recommendations will be made for managing conflicts.

10.5 ABBREVIATIONS

Abbreviation	Term
ACOG	American College of Obstetricians and Gynecologists
AE	Adverse Event
APP	Proprietary Mobile Application
BMI	Body Mass Index
BPM	Beats Per Minute
BT	Bluetooth
BLE	Bluetooth Low Energy
CCM	Cloud Computing Module
CE	European Conformity
CL	Cervical Length
CRC	Clinical Research Coordinator
CRF	Case Report Form
CTG	Cardiotocography
DPE	Data Processing Engine
IRB	Institution Review Board
ECG	Electrocardiogram

Abbreviation	Term
EEG	Electroencephalography
EHG	Electrohysterography
EMG	Electromyography
EUM	Electrical Uterine Myography
FCC	Federal Communications Commission
FDA	Food and Drug Administration
FHR	Fetal Heart Rate
FSE	Fetal Scalp Electrode
GCP	Good Clinical Practice
GDM	Gestational Diabetes mellitus
HIPAA	Health Insurance Portability and Accountability Act
HTN	Hypertension
HW	Hardware
ICF	Informed Consent Form
IFU	Instructions for Use
IP	Investigational Product
IRB	Institutional Review Board
IUPC	Intrauterine Pressure Catheters
LOA	Limits of Agreement
M•CARE™	Marani Health M•care™ System
M•CORE™	Marani Health M•core™ controller
M•WRAP™	Marani Health M•wrap™ wearable band
MA	Mobile Application
MD	Medical Doctor
ME	Management Engine
MHR	Maternal Heart Rate
NST	Non-Stress Test
PA	Performance Analysis
PCG	Phonocardiography

Abbreviation	Term
PI	Primary Investigator
RTTI	Run-Time Type Information
SA	Safety Analysis
SAE	Serious Adverse Event
SW	Software
TOCO	Tocodynamometry
UA	Uterine Activity
UADE	Unanticipated Adverse Device Effect
UC	Uterine Contractions

10.6 DEFINITIONS

Term	Definition
Adverse Event	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in subjects, users, or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated. *(ISO 14155:2020, section 3.2)*
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling. This definition includes device deficiencies related to the investigational medical device or comparator. *(ISO 14155:2020, section 3.19)*
Device Malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the Instructions for Use, study protocol, or Investigator's Brochure. *(ISO 14155:2020, section 3.33)*
SAE	An adverse event that led to: a) Death b) A life-threatening illness or injury c) Permanent impairment of a body structure or body function including chronic diseases d) In-patient or prolonged hospitalization e) Medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function f) Fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment

Term	Definition
	(ISO 14155:2020, section 3.45)
Unanticipated Adverse Device Effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. *(21 CFR 812.3(s))*

10.7 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes with versions of the protocol, including a description of the change and rationale.

Version	Date	Description of Change	Brief Rationale
B	07JUL2021	Initial IRB-approved version	N/A
C	29DEC2021	Addition of a third group to the study population to include a Research Visit group, defined as subjects scheduled for research visits in a non-clinic setting with oversight by a clinical practitioner.	Inclusion of the Research group was done to reflect the non-clinic study setting
D	17FEB2022	• Section 1.2 'Study Flow' figure updated to revise step prior to the 'Place M·wrap' to include reference to the IFU. • Revisions to Exclusion Criteria #2 & #7 • Updates to Section 6.1 to clarify process flow • Section 10.5 updated to include abbreviation for Instructions for Use (IFU) • Appendix 12.1 'Study Flow' figure updated as referenced in 1st bullet above	Reference Instructions for Use (IFU) where applicable; revisions to Exclusion Criteria for consistency with IFU; clarify study administration process flow.

Version	Date	Description of Change	Brief Rationale
E	22JUN2022	• Added protocol agreement form at front of document	Alignment with GCP
		• Synopsis and Section 5.4 updated to redefine group definitions	Alignment with statistical analysis plan (Section 9); no changes to the overall study population or methods for recruitment/research conduct
		• Synopsis and Section 5.2 updated to add an additional exclusion for subjects with history of skin allergies to cosmetics and lotions	Added to ensure exclusion of patients who may be allergic
		• Synopsis and various places throughout Sections 3 and 9 updated to move UC sensitivity from primary to secondary endpoint	Updated regulatory strategy
		• Synopsis and Sections 3 and 9 updated throughout	Consistency between sections
		• Added section 3.1, Objective	Consistency with synopsis and Section 9
		• Removed reference to undefined term “Unanticipated Problems” throughout the document, replaced with the more appropriate term (e.g., adverse event, device deficiency) when applicable	Consistent use of FDA and ISO 14155:2020 GCP defined terminology
		• Section 7.1 updated to remove reference to subject replacement	Replacements will not be utilized for this study
		• Section 8.3.1 updated to remove reference to 21 CFR 312 and clarify applicable medical device	21 CFR 312 was written in error and is not applicable to medical device studies; medical monitor not

Version	Date	Description of Change	Brief Rationale
		definitions, removed reference to medical monitor review	necessary for a non-significant risk study
		• Section 8.3.2 updated to replace "failures and malfunctions" with "device deficiencies"	Using preferred term per ISO 14155:2020 GCP, which includes both device failures and malfunctions
		• Reference to ISO 14155:2020 GCP added where applicable throughout the document	ISO 14155:2020, *Clinical investigation of medical devices for human subjects – Good clinical practice*, will be followed for this study
		• Section 10.4.5 updated to remove reference to Good Laboratory and Good Manufacturing Practices (GLP and GMP)	GLP and GMP are out of scope for what clinical monitors will verify.
		• New Section 10.6 added to provide definitions of common safety terminology used throughout the document	Consistency of terminology and compliance to common regulatory definitions
		• Added missing references and corrected errors in citations throughout the document, updated bibliography in section 11	Accuracy of scientific rationale
		• Appendix 1 (Study Setup and Monitoring Flow) deleted	Redundant with Section 1.2
		• Added appropriate references to tables, figures, and appendices throughout the document • Minor corrections and deletion of redundant phrases throughout the document	Readability, clarity, and consistency across the document

Version	Date	Description of Change	Brief Rationale
F	26-SEP-2022	• Correction to study center name in synopsis	Error correction
		• Changed “clinical practitioner” to “healthcare professional” throughout the document	Provide clarity of oversight of research-only study center
		• Inclusion criterion #7 changed from “≤ 130 cm” to “≤ 135 cm”	Error – criterion corrected to match M•wrap sizing chart
		• Corrected wording throughout to clarify differences between research-only visits and visits occurring in a clinical setting	Accuracy of requirements based on type of study center
		• Section 10.1: Removed “$70” as the subject renumeration amount	Renumeration type will be set forth by the reviewing IRB and may vary across study centers
G	13-Dec-2022	• Synopsis and Section 9.5: Updated total enrollment number from 115 to 130	Increase in total enrollment maximum to allow for flexibility in anticipated 30% fallout rate.

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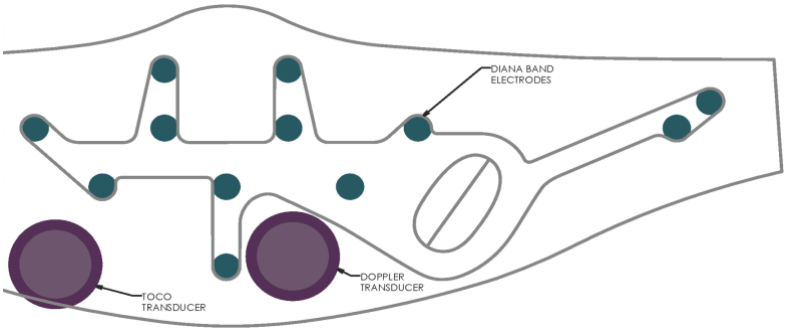
12 APPENDICES

APPENDIX 1 – M•WRAP CONFIGURATION FOR CONCURRENT CTG USE

Marani Health proposes a series of performance data testing to support the substantial equivalence determination. The M•wrap capabilities of accurately recording with high fidelity the FHR, MHR and UC will be determined by comparing our system to the reference device, the Philips Avalon FM 20, FM30, FM40, or FM50.

A segment of the M•wrap compression garment fabric will be cut out to enable simultaneous recording of FHR, MHR and UC with the M•wrap and the Philips Avalon FM 20, FM30, FM40, or FM50. The below image is a representative graphic of the M•wrap and possible locations for the TOCO and Doppler Transducers.



These TOCO and Doppler transducers will be placed in the available garment material and will not affect the integrity of the electrodes and wires. The M•wrap contains spaces consisting of textile fabric only which is around the inlay section in which CTG transducers can be located without interfering with the device. The figure below shows possible placements for the CTG transducers, labeled A – F. There are six broad positions within the garment that can accommodate CTG placement, with some flexibility in each area that will allow for placement optimization.