Study Protocol

Clinical Study Evaluating the Safety of PregSense™ and Comparative Performance of PregSense™ versus CTG in Prenatal Monitoring of Pregnant subjects

Protocol Number: CLP1000

Test Product:	**PregSense™**
Sponsor's Name: **Sponsor's Address:**	**Nuvo Group Ltd.** **11th Menachem Begin Rd., Ramat Gan 5268104, Israel**
Sponsor's Telephone Number: **Sponsor's Fax Number:**	Tele# (+972).3.624.2266 Fax# (+972).3.529.4072
Study Number and version: **Version Date:**	CLP1000 rev #05 May 2018

CONFIDENTIAL

Approval Table:

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Prepared by	Iris Stein Shalev	Clinical Trials Manager		
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Summary of Changes History:

Revision No.	Description of Changes	Release date
01	New document	Same as last signature date
02	• Updates to Standards • Update Illustrations & block diagrams • Statistical analysis update • Presentation App – MD output • Editorial changes • Additional table of figures • Additional appendix - Pivotal study setup flow	Same as last signature date
03	• Update Presentation App output (page 22-23)	Same as last signature date
04	• Change Pilot to Pivotal • Screening update (section 5.1.1) • Recording session update (section 7.2) • Statistical analysis update (sections 9) • Editorial changes	Same as last signature date
05	• Statistical analysis update following FDA recommendation (section 9) • The term "gold standard" was changed to "standard of care" as per FDA request. • Increased the number of blinded assessors from 2 to 3 regardless discrepancy of assessment • Removed UA from intended of use and kept it in the secondary end-point for data collection purpose • Editorial changes	Same as last signature date

Distribution of Controlled Copies:

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Investigators' Statement

I have read the protocol:

Clinical Study Evaluating the Safety of PregSense™ and Comparative Performance of PregSense™ versus CTG in Prenatal Monitoring of Pregnant subjects

That contains all information necessary to the conduct of the study. I agree to conduct the study as outlined therein and in accordance with ISO 14155 Clinical Investigation of Medical Devices for Human Subjects.

The undersigned confirms that they agree to conduct the study under the conditions described in this protocol:

_____ |__| |__| / |__| |__| / |__| |__|

Principal Investigator (Print Name) Date (dd / mm / yy)

_____

Principal Investigator's Signature

Address:

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STUDY SYNOPSIS

Protocol Number	CLP1000
Study Title:	Clinical Study Evaluating the Safety of PregSense™ and Comparative Performance of PregSense™ versus CTG in Prenatal Monitoring of Pregnant subjects.
Number of Centers:	Up to 5 centers with possible extension
Countries:	Israel, Germany and USA
Study Duration:	The expected total duration of the study for each subject is up to 2 hours as follows: Enrollment: Gestational age >32+0 weeks Data collection: 1st data collection session and optional additional sessions between the initial session and up to labor.
Total Study Duration:	~24 months
Expected Subject Enrollment:	The total expected enrollment is up to 200 subjects.
Study Population:	Pregnant women with singleton gestation > 32+0 weeks of pregnancy.
Study Objectives:	The primary objective of this research is to assess the agreement between PregSense™ data collection, and values measured via the standard of care used for prenatal monitoring (i.e. CTG) and to assess the safety of PregSense™.
Study Design:	This will be a multi-center, prospective, comparative, open label study. <u>Screening:</u> Confirmation of the eligibility criteria will be performed. Eligible subjects will be included into the study. • Consent and recruitment • Subject preparations • The sensors will be attached on the subject's abdomen <u>Recording session:</u> The subject will undergo continuous recording using PregSense. Additional recording with the standard of care (CTG - Cardiotocography) will be done, including, but not limited to, ECG (Electrocardiogram), non-stress test and uterine contractions recording. In addition (if applicable), clinical tests, clinical scores, medications, fluids and imaging data and its interpretation will be collected. Offline analysis: The data will be collected and downloaded. Comprehensive analysis of the values will be performed offline. Safety assessment:

	The subject will undergo continuous monitoring by the medical team to identify any safety issue, including but not limited to, irritation, sensitization and potential harmful misuse.
Inclusion criteria:	1. Female age between 18-50 2. Gestational age >32 + 0 weeks 3. Singleton gestation 4. Ability to understand and sign informed consent
Exclusion criteria:	1. BMI ≥45 and 15≤ prior pregnancy (Body Mass Index) 2. Multiple gestation 3. Uncontrolled Hypertension 4. Fetal Anomaly 5. Subjects with skin problems in the abdominal area (such as flesh wounds, cuts in the skin, skin rashes, etc.) 6. Subjects with implanted electronic devices (pacemaker, defibrillator, etc.) 7. Subjects who, in the judgment of the investigator, are likely to be non-compliant or uncooperative during the study
Medical Device Description:	PregSense™, developed and designed by Nuvo Group, consists of the following three basic components: (1) Wearable device – containing; a. The sensors module (WSB- Wearable Sensory Belt) b. The major electronic module (WSH - Wireless Sensing Hub) (2) Mobile Application (MA) – a. Gateway Service Application b. Presentation Application: i. MD Application: ii. ME Application: (3) Cloud based application PregSense™ will include the following features [Please note, in PregSense Apps (ME, MD or Pivotal Study App) the features might be presented in alignment with the end user requirements]: • FHR (Fetal Heart Rate) • MHR (Maternal Heart Rate) • Fetal heart rate response (Fetal Activity) (in PregSense ME App) • Maternal Activity (in PregSense ME App) • Uterine Activity (Uterine Contractions, if applicable) Note: For this Pivotal study, a subversion of the Application with study metrics only will be applied, in order to show the agreement between PregSense and the standard of care device (i.e. CTG).
Study Endpoints:	<u>Primary Performance Endpoints:</u> • Fetal HR

	• Maternal HR Safety Endpoints: • Safety, tolerability and compliance with PregSense™ in pregnant women with singleton pregnancy > 32 + 0 weeks of gestation. • All adverse events and serious adverse events related and unrelated to PregSense use. As collected via PregSense™ and the data collected via the standard of care monitoring system (i.e. CTG). <u>Secondary Performance Endpoints:</u> • Uterine contractions As collected via PregSense™ and the data collected via the standard of care monitoring system (i.e. CTG).

LIST OF ABBREVIATIONS

ACOG - American College of Obstetricians and Gynecologists
ADR – Adverse Device Reaction
AE – Adverse Event
APP - Proprietary Mobile Application
BMI – Body Mass Index
BT- Bluetooth
CCM - Cloud Computing Module
CE - European Conformity
CL – Cervical Length
CRC – Clinical Research Coordinator
CRF – Case Report Form
CTG – Cardiotocography
DPE - Data Processing Engine
EC/IRB –Ethic Committee/Institution Review Board
ECG – Electrocardiogram
EEG – Electro - Encephalography
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
HW – Hardware
HIPAA - Health Insurance Portability and Accountability Act
LOA - Limits of Agreement
ICF – Informed Consent Form
IP – Investigational Product
IUPC – Intrauterine Pressure Catheters
MA – Mobile Application
MD – Medical Doctor
ME – Management Engine

MHR – Maternal Heart Rate
NST – Non-Stress Test
PA – Performance Analysis
PCG - Phonocardiography
PI – Primary Investigator
RTTI - Run-Time Type Information
SA – Safety Analysis
SW – Software
TOCO – Tocodynamometry
UA – Uterine Activity
UC – Uterine Contractions
US – Ultra Sound
WSB – Wearable Sensory Belt
WSH – Wireless Sensory Hub

1 INTRODUCTION

1.1 Background

Pregnancy brings a variety of health risks to women as well as to their unborn child. In the US, among the ~ 4 million deliveries each year, 94.1% list some type of pregnancy complication[1]. Complications and pregnancy symptoms range from mild and annoying discomforts to severe illnesses, sometimes even life-threatening. There are times when where it is difficult for a woman to determine which symptoms are normal and which are not[2][3].

Pregnant women have limited opportunities to expand their understanding of their fetus's development in utero. Besides the monthly checkups with their doctor, pregnant women will remain unaware of their fetal's activities. The mother wants information, comfort and the confidence that she is doing everything she can to complete a healthy pregnancy and to create additional opportunities to learn about and bond with her developing fetus.

Secondarily, mother herself is going through many physiological changes that result in differing sleeping patterns, activity levels, and sleep cycles. Importantly, she wants to know how her activities impact her developing fetus[4].

Current clinical assessment of potential fetal distress during pregnancies is done through in-frequent monitoring of the vital signs of mother and unborn child. Existing technologies e.g. Ultra Sound (US) Doppler us, are used in an out-clinical setting and in some cases in a clinical setting. None of these technologies are used continuously. Also, these technologies typically use only one biomarker (e.g. cardiac state), do not occur in real-time and involve survey-based information from the mother. The fetal heart rate is currently the standard of care to tell whether the fetal is doing well or may have some problems.

In addition, the poor inter-and intra- observer variabilities in the interpretation of FHR tracing have been known as one of the major drawbacks of the CTG monitoring[5]. For example, when 4 obstetricians examine 50 CTGs, the agreement was reported as only 20% of the cases[6]. The visual interoperation of CTG traces seems to be a major cause. Computerized CTG is a method to analyze FHR patterns in terms of a computer algorithm to improve CTG interpretation by making up poor inter and intra-observer.

Doppler-based technology has been the standard of care in pregnancy monitoring for 40+ years, influencing the vast majority of home pregnancy monitors available today. Wearable health technology has become much more prevalent in everyday lives, with companies like FitBit, Pebble, Jawbone, and Apple Watch paving the way for personal health and wellness trackers as commonplace devices. However, a viable and accurate wearable pregnancy solution that does not use Doppler-technology, and can therefore be used safely and continuously, is not yet on the market.

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

External Monitoring: External monitoring is usually being done at different times during the pregnancy, and/ or during labor.

External monitoring can be done by listening to the fetal heartbeat with a stethoscope. More often, external monitoring is done using two flat devices (sensors) held in place with elastic belts on the belly. One sensor uses reflected sound waves (ultrasound) to keep track of the FHR. The other sensor measures the contractions

[1] Healthcare Cost and Utilization Project: Complicating Conditions of Pregnancy and Childbirth, 2008
[2] Pregnancy Complications; Centers for Disease Control and Prevention
[3] If You Do Not Ask, They Will Not Tell: Evaluating Pregnancy Risk in Young Women in Pediatric Hospitals: Journal of Adolescent Health
[4] Fetal Monitoring: Creating a Culture of Safety With Informed Choice
[5] Inconsistencies in classification by experts of cardiotocograms and subsequent clinical decision.
[6] Intra- and inter-observer variability in the assessment of intrapartum cardiotocograms.

duration. The fetal heartbeat may be heard as a beeping sound or printed out on a chart. The frequency and duration of the uterine contractions are usually printed out on a chart.

In addition, external monitoring is used for a non-stress test (NST), which records the fetal heart rate while the fetal is moving and not moving. The primary goal of the test is to measure the heart rate of the fetus in response to its own movements. Healthy babies will respond with an increased heart rate during times of movement, and the heart rate will decrease at rest. The concept behind a non-stress test is that adequate oxygen is required for fetal activity and heart rate to be within normal ranges.

A non-stress test may be combined with a fetal ultrasound to evaluate the amount of amniotic fluid.

External monitoring is also done for a contraction stress test (CST), which records changes of the fetal heart rate during uterine contractions. It is performed near the end of pregnancy to determine how well the fetus will cope with the contractions of childbirth. The aim is to induce contractions and monitor the fetus to check for heart rate abnormalities using a cardiotocograph. A CST is one type of antenatal fetal surveillance technique. It may help predict the fetal capability to tolerate the stress of labor and vaginal delivery[7].

The biggest advantage of Cardiotocography (CTG) is that it is an external device. The disadvantage is its inability to give an accurate reading on intrauterine pressure and activity. Without intrauterine pressure capability the CTG is not an indicated device for augmentation of labor. The CTG's readings can not only be influenced by intra-amniotic pressure but by local uterine muscle tension and abdominal wall flexing, etc. It is hampered by the thickness of the abdominal wall, which is why there is a high rate of failure in high BMI Moms.

Overall, in high BMI moms the accuracy in CTG is poor. Furthermore, the best position for CTG is supine, which is not desirable for the subject and limits mobility. The technology has remained essentially unchanged since 1968.

Internal monitoring; "Intrauterine pressure catheters (IUPC) and fetal scalp electrodes (FSE) are commonly used devices for intrapartum monitoring and management. Although the internal monitors used are sterilely packaged, they travel through the vaginal canal into the uterine cavity, providing a potential pathway for contamination and ascending infections[8].

Internal monitoring can be done only after the cervix has dilated to at least 2 centimeters (cm) and the amniotic sac has ruptured and if the ECG cannot be performed as part of the routine gold standard.

2 STUDY RATIONALE

PregSense™ provides accurate, real-time and continuous information on fetal and maternal parameters, without compromising the subject's and fetus's safety. Application and set-up take only minutes, shortening the time of data collection. The non–invasive PregSense™ brings a much-awaited breakthrough in the field of maternity monitoring.

PregSense™ is based on measurements of fetal and maternal wellbeing including: fetal movements, maternal & fetal cardio-vascular activity and uterine contractions. The clinically validated mature wearable system will simultaneously record both fetal and maternal parameters non-invasively for extended periods of time. The product provides robust parameter measurements compared to the standard of care monitoring device for home use.

[7] Fetal Heart Monitoring: John Hopkins Medicine
[8] External and Internal Heart Rate Monitoring of the Fetus: University of Rochester School of Medicine

3 DEVICE DESCRIPTION

3.1 Intended Use

PregSense™ is a maternal-fetal monitor that non-invasively measures and displays fetal heart rate (FHR) and maternal heart rate (MHR). PregSense™ acquires and displays the FHR & MHR tracing from abdominal surface electrodes that pick up the fetal ECG (fECG) and maternal ECG (mECG) signal, and surface acoustic sensors that pick up the fetal PCG (fPCG) and the maternal PCG (mPCG) signals.

PregSense™ is indicated for use on women who are >32 gestational weeks, with singleton pregnancies, using surface electrodes on the maternal abdomen. PregSense™ maternal-fetal monitor is intended for use by healthcare professionals in health care facilities and by the patient in the patients' home on the order of a physician.

This system does not prevent the onset of preterm labor nor will it prevent the occurrence of preterm birth.

Intended population:

- Pregnant women with a singleton pregnancy >32 + 0 weeks of gestation.

3.2 Data flow diagram between the main components of PregSense™:

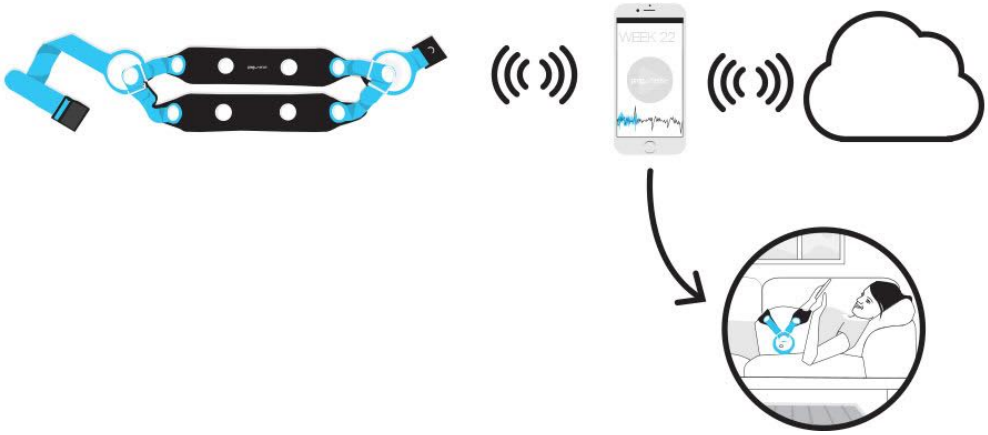


Figure 1 PregSense ME (self-monitoring)

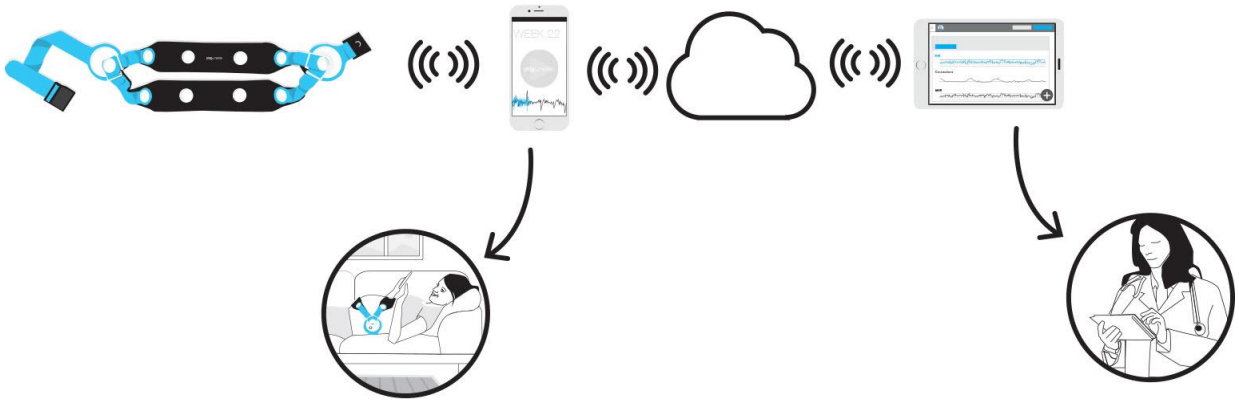


Figure 2 PregSense MD (remote monitoring)

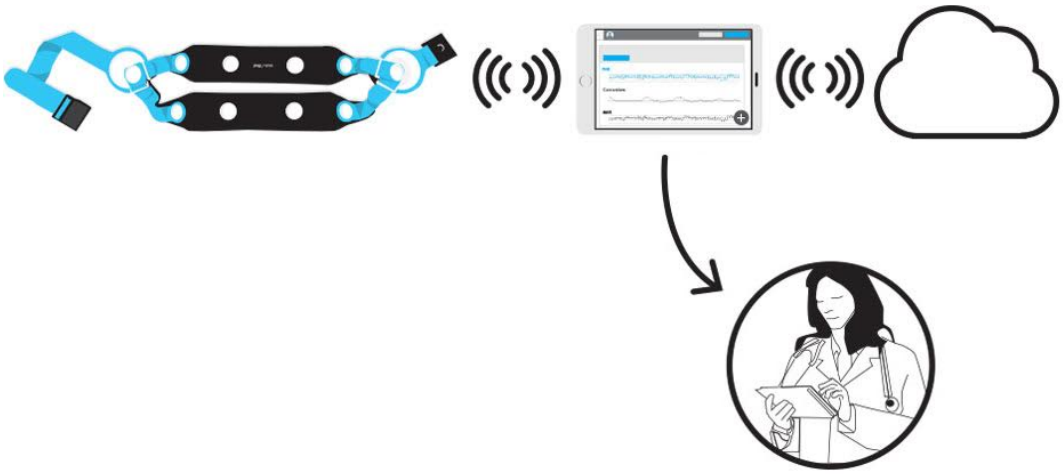
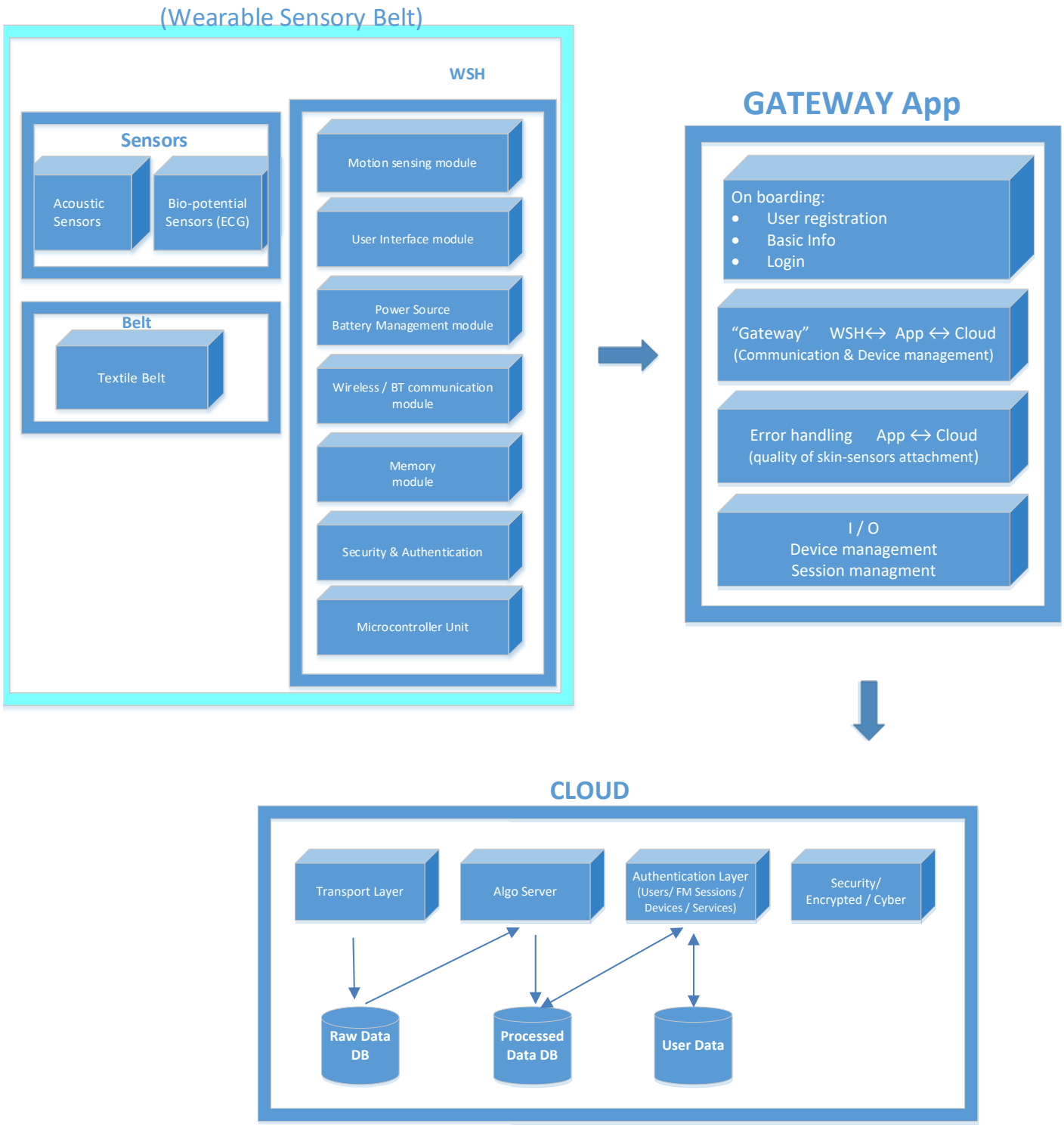


Figure 3 PregSense MD (Medical center/Clinic environment)

3.3 The system

Figure 4 Block Diagram of PregSense™ Components



PregSense™ - developed and designed by Nuvo Group Ltd., consists of the following three main components:

(1) Wearable device containing;

a. The sensors module (WSB- Wearable Sensory Belt)

b. The major electronic module (WSH - Wireless Sensing Hub).

(2) Mobile Device Application (MA);

a. Gateway Service Application

b. Presentation Application:

i. MD Application

ii. ME Application

(3) Cloud based application

3.3.1 Wearable device

The Wearable device incorporates wearable sensors and electronics for data acquisition, data storage and communication.

The Wearable device contains the following compartments:

3.3.1.1 Wearable Sensory Belt (WSB)

The passive, non-invasive sensors located on the abdomen above and below the womb and held in position by two comfortable, expandable and adjustable textile straps.
The Wearable Sensory Belt is composed of 2 elements:

a. **Textile Belt** (see figure 2):
The textile belt is designed to allow good attachment of sensors to the woman's abdomen and for maximum comfort; its adjustable circumference range is approximately 60 -150 cm.

b. **Sensors:**

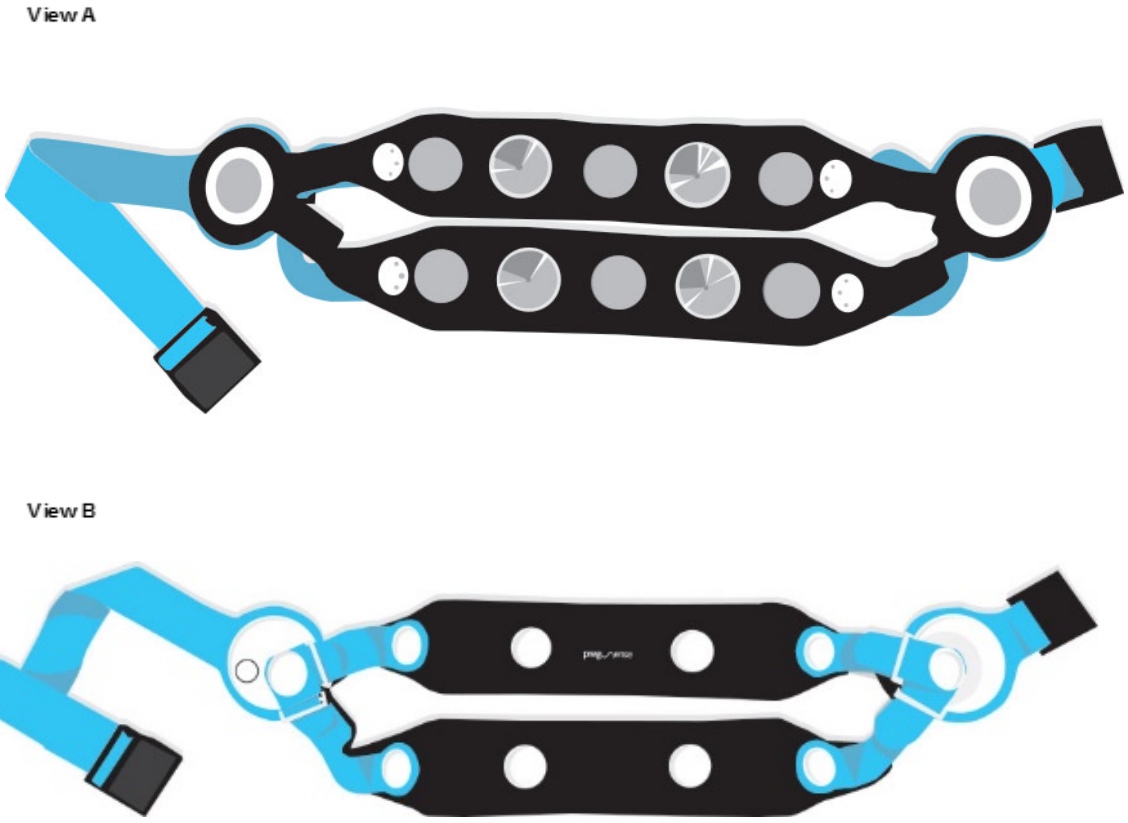
The sensors are divided into 2 types; Acoustic and Bio-potential.

- Acoustic - The acoustic sensor was developed and designed by Nuvo Group Ltd., and for maximum patient safety, the electrical parts are isolated from the patients' body. The acoustic sensors are essentially highly sensitive components transducing acoustical pressure into electrical voltage. The sensors' acoustic properties are designed for maximum performance. The inner microphone is carefully selected to match the working environment. It replicates the concept of electronic stethoscope, but rather than using a single sensor that cannot follow fetal movements in the womb, there are four sensors symmetrically distributed in four locations on upper and lower parts of the abdomen – two on each side – attached to the body with the textile belt.
- Bio-potential - The bio-potential sensor was developed and designed by Nuvo Group Ltd. for collecting the electrical signals from the skin with maximum patient safety and comfort in a manner that resembles ECG, enabling continues recording of the electrical activity of the heart. These sensors detect the tiny electrical changes on the skin that arise from the heart muscle's electro-physiological pattern of depolarizing during each heartbeat. The measured signals are the potential difference between two selected points on the body, called "leads".

The bio-potential signals come from the subject's heart and mainly the fetus's heart. However, due to their sizes and strength, the bio-potential signals coming from a given subject's heart are three orders of magnitude (i.e. 1,000 times) stronger than the fetus' signals. The maternal and fetal heartbeats are not

synchronized, and typically the fetal heartbeat is much faster (about twice) than the heartrate of the pregnant subject.
The shape of the sensor suits the pregnant woman's abdominal curvature. The bio-potential sensor is designed to maximize the contact area with the skin in order to produce a high-quality signal.

Figure 5 *Schematic Illustration of the Wearable Sensory Belt*



View A –Inner view of the PregSense™ Wearable Sensory Belt,

View B – Outer view of the PregSense™ Wearable Sensory Belt

3.3.1.2 Wireless Sensing Hub (WSH)

The WSH intends to acquire the signals from the sensors, transform it and transmit it to a nearby smartphone/Tablet.
The module consists of three main parts: Analog Front-End Module (AFEM), Analog-to-Digital Conversion Module (ADCM) and Wireless Communication Module (WCM). The AFEM provides initial signal conditioning, including impedance matching, amplification, and bandwidth filtering. The module further – ADCM incorporates the Analog to Digital Converter which converts the data from analog to digital domain and then a Wireless Communication Module which transfers the data to a nearby (up to 10 meters) mobile device (smartphone or tablet) using Bluetooth® technology. The module, as the rest of the product, complies with FCC, CE and RTTI standards.

PregSense™ is powered by a rechargeable battery and equipped with a battery charger cable. PregSense ™ is not operable while charging the battery.

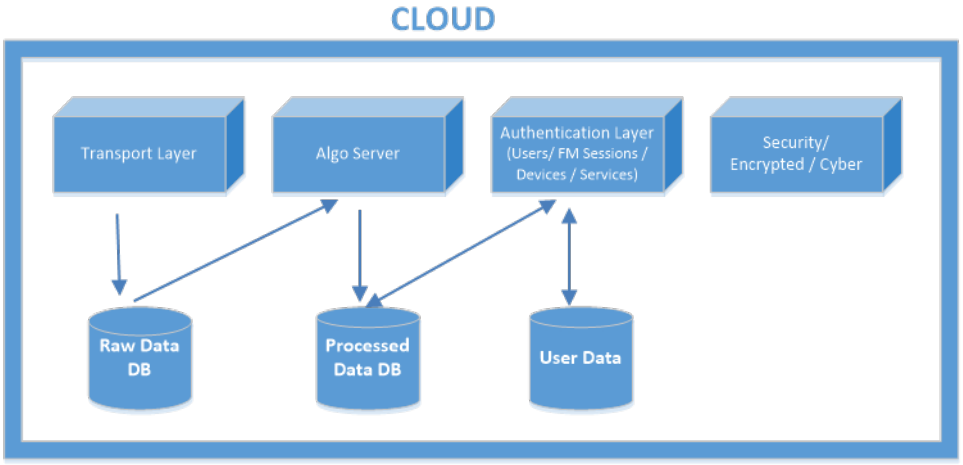


Figure 6 *PregSense data flow of the cloud*

3.4 Cloud

Cloud-based modules, which includes also data-bases management, are running on servers operated by a major cloud service provider, such as Amazon Web Services by Amazon Inc. or similar. It leverages the essential services provided by the Cloud service provider, such as security, privacy, redundancy, scalability, etc.

This component receives the data from the PregSense Mobile Application (MA) and performs the proprietary signal processing.

3.4.1 Transport Layer & Raw data management

This module handles the incoming raw data and meta-data from the MA by verifying the reception of all data, including completing missing data due to communication errors, and stores the data in Raw Database Meta-data includes, but not limited to;

a) user-name and other IDs

b) belt UDI

c) WSH – Mac address

d) time tag (for all stored data) - year, month, day, hour, minute, second (of each session form the first session start to last session end)

3.4.2 Data Processing

The cloud receives the data from the application (MA) and performs the proprietary signal processing, which leads to a clear fetal and maternal cardiac activity signal and uterine contractions signal. Merging (or fusion) of the outcome of the Bio-potential (after processing) and the acoustic sensors/Phonocardiogram (PCG) (after processing) is performed by comparing the results at the cloud algorithms. The algorithm enables the inference of the Fetal Heart Rate (FHR).

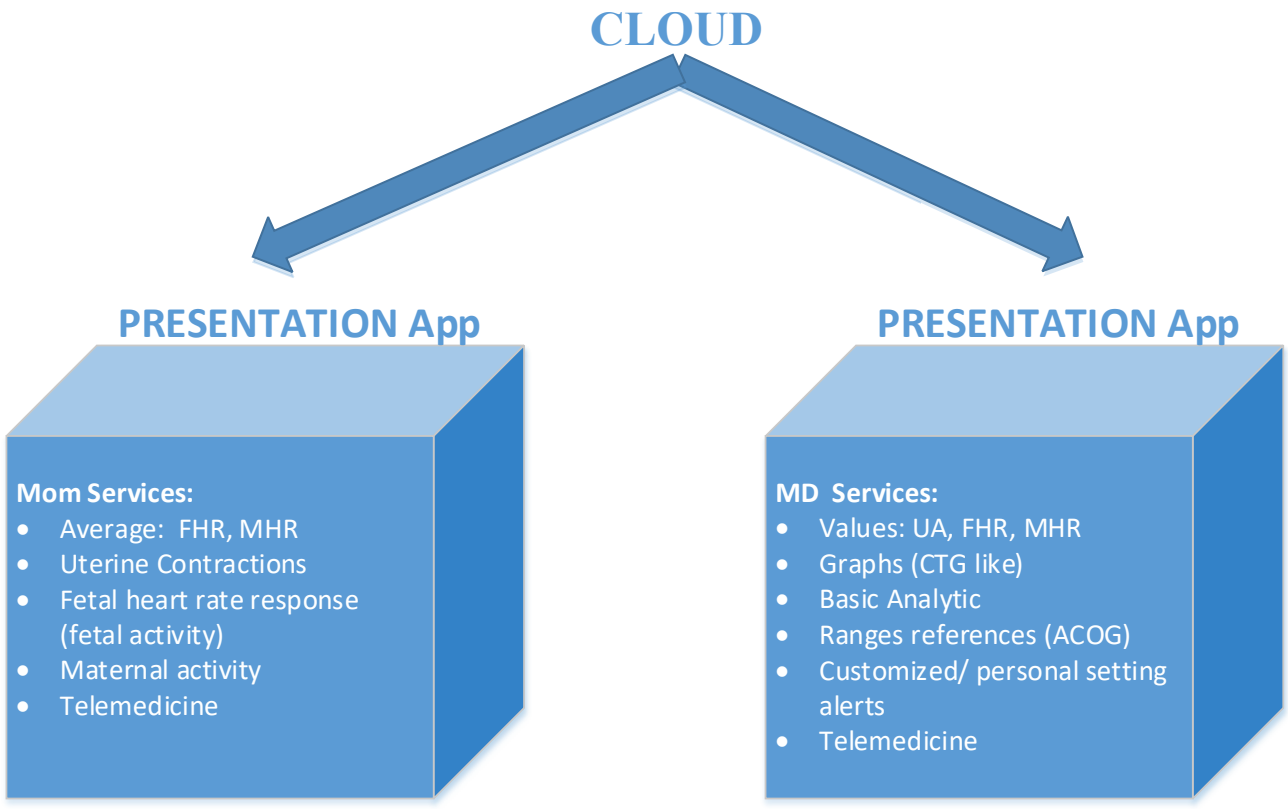


Figure 7 *PregSense data flow from the cloud to the App*

3.5 Mobile Application (MA) – Gateway Service Application

The MA transfers a combined sensory data from the Wearable Device in real-time to the cloud for processing. The role of this part of the system is to handle the data communication between the Wearable Device and the Cloud verifying that the information is received properly and safely, assuring continuous reliable connection with minimum interruption.

A tablet/smartphone typically has three wireless communication channels: a) Bluetooth b) Wi-Fi and c) Cellular phone network:

- Bluetooth serves for communication with the wearable device.
- Wi-Fi serves as communication channel with the Cloud. It will utilize the local Wi-Fi network and router. Wi-Fi is the Default channel.
- Cellular phone network – serves as backup communication channel in case the Wi-Fi is either not available or does not function properly.

This dedicated mobile application enables easy usage by the mother as well as full control of the device. The application will also be in charge of the protection of the data when it is sent from the sensors over Bluetooth (BT) and when it is sent to the cloud computing module (CCM) via TCP/IP. Full compliance with medical data security will be employed.

There are two mobile applications used with PregSense™: PregSense MD and PregSense ME. Additionally, there is a dedicated App for this Pivotal study, which was developed in order to show an agreement between the standard of care monitoring system (i.e. CTG) and PregSense, as described below:

3.5.1 MD Application:

This application is used by healthcare personnel on a mobile device (smartphone/tablet) or stationary device (PC) in order to monitor the pregnant patient. The MD App will present the following parameters:

- FHR – figures presented as beat/min + graph (of the entire session) MHR - figures presented as beat/min + graph (of the entire session)
- Uterine Activity (Uterine Contractions, if applicable)
- Customized/ personal setting – Alerts (to be managed by the physician)
- Ranges reference (according to ACOG)
- Telemedicine

3.5.2 ME Application:

This application is used by pregnant women on a mobile device (smartphone/tablet).

PregSense™ Mom App presents the following parameters:

- FHR average (per min) + Ripples[9]
- MHR average (per min) + Ripples
- Fetal Heart Rate response (presented as Fetal activity[10])
- Maternal Activity
- Uterine Contractions (if applicable)
- Telemedicine

Telemedicine: the pregnant women and her assigned doctor/medical supervisor can share the monitored data and communicate via telemedicine and can:

- Enable access to session's data from remote location
- Perform audio/video chat option

For this Pivotal study, and in order to assess the agreement between PregSense™ data collection, and values measured via the standard of care used for prenatal monitoring (i.e. CTG) and to assess the safety of PregSense™ (as per study endpoints). A dedicated study App will be applied with the following parameters:

- Synchronous log of PregSense and the CTG, recording data to the cloud (for agreement purposes between both devices)
- Subject demographic details screen (in accordance with GCP guidelines)
- Real time events insertion (for safety evaluation)
- Graph summary per session (CTG like)

[9] "Ripples" - a graphic presentation of the heartbeat, excluding any figures or any quantitative information.
[10] A derivative of FHR analysis

3.6 Device safety - Compliance Pre-clinical

3.6.1 Compliance and Pre-Clinical

The pre-clinical testing that was performed on PregSense is described hereunder:

(1) Electrical Safety testing:
- EN 60601-1:2006/A1:2013 [EU harmonized version] & ANSI/AAMI ES60601-1:2005/(R) 2012 and A1:2012, C1:2009/(R) 2012 and A2:2010/(R) 2012 [FDA recognized version] Medical electrical equipment - General requirements for basic safety and essential performance.
- IEC 60601-1-11: 2010 /IEC 60601-1-11: 2015 Medical electrical equipment - General requirements for basic safety and essential performance - Collateral standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment

(2) EMC:
- EN 60601-1-2: 2007 [EU harmonized version] & IEC 60601-1-2: 2007 [FDA recognized version] Medical electrical equipment - General requirements for basic safety and essential performance – Collateral standard: Electromagnetic compatibility - Requirements and tests (FDA also recognizes the 4th edition of this standard, IEC 60601-1-2: 2014.
- FCC CFR 47

(3) Biocompatibility testing:
Nuvo PregSense sensors are produced under ISO 13485 quality system. The sensors were tested for biocompatibility according to ISO 10993-1, ISO 10993-5 for:
- In-vitro cytotoxicity

(4) Batteries:
- UL 1642 5th edition for Lithium Batteries.
- IEC 62133: 2012 Secondary Cells and Batteries Containing Alkaline or Other Non-Acid Electrolytes - Safety Requirements For Portable Sealed Secondary Cells, And For Batteries Made From Them, For Use In Portable Applications.

(5) Tests performed by Nuvo Group:
- Each Software version of the system is verified according to the Software standards ISO 60601-1 section 14 and ISO 62304.
- FDA Guidance document – General principles of software Validation: Final Guidance for Industry and FDA Staff.
- Each system undergoes strict functionality testing before release according to written test procedures.

3.6.2 Previous Clinical evaluation

A study evaluating the Fetal Heart Rate (FHR) data recording for developing a continuous FHR monitoring using a designated sensory belt was conducted in Hadassah Hospital, Jerusalem, Israel. This study was conducted to assess the feasibility and safety of PregSense™.
During the feasibility study a total of 76 subjects participated for which a total of 510 recording session were executed. Female subjects aged ≥ 18 years and ≤ 50 years with singleton pregnancy between 20-40 weeks' gestation and who were capable of signing informed consent were included in the study.
PregSense™ was recorded simultaneously with the industry standard BIOPAC™ MP-150 bio-medical data acquisition system. No adverse events, procedure-related or device-related, were reported during the study.

3.7 Risk Management analysis

Risk Analysis was performed according to the guidelines of the Risk Management Standard ISO 14971:2012 / ISO 14971:2007 Medical devices - Application of risk management to medical devices.

- All risk control measures have been implemented and verified. The overall residual risk for the device has been found to be acceptable using the criteria defined in the risk management plan.
- A review of the individual risks against the benefits of the device indicates that the benefits of the device outweigh the risks involved in all cases.

For further risk analysis information, please see the section 11.2 in the Investigator Brochure

4 STUDY ENPOINTS

4.1 Primary Performance Endpoints:

The primary performance endpoints will include:

- Fetal HR

Maternal HRBoth endpoints will be collected via PregSense™ and via the standard of care monitoring system (CTG).

4.2 Safety endpoints:

Incidence of device related and/or protocol procedure related adverse events and/ or serious adverse events related to the study device, in pregnant women with singleton pregnancy > 24 + 0 weeks of gestation.

4.3 Secondary Performance Endpoints:

The secondary performance endpoints will include:

- Uterine contractions

PregSense™ also acquires and displays the UA (Uterine contractions) tracing from the uterine Electrohysterography (EHG) signal.
Contractions will be collected via PregSense™ and via the standard of care monitoring system (CTG).

5 STUDY DESIGN

5.1 Study Overview and plan

This study is a prospective, open label, comparative, multi-center study.

This study will be performed to collect and digitally record data from PregSense™, and the standard of care (CTG) in order to provide evidence of safety and agreement between PregSense™ and the standard of care devices (for further information see section 6.1.2, and 8.2).

During the study conduct, Nuvo Group will continuously review adverse events and will meet (as needed) periodically to review the accumulated safety data (for further information, see section 9).

5.1.1 Screening

An initial subject screening evaluation will be done during consultation or on the phone in order to identify eligible candidates. This will be applied on all trial subjects.

The candidate will then be invited to the first visit in which, confirmation of the eligibility criteria will be performed. All screened subjects will be identified by a subject number and will sign an Informed Consent Form (ICF) prior to any study procedure initiation. Each subject will receive a detailed explanation about the study purpose and procedure; at the end of the explanation, the

subject will sign an ICF. An authorized study personnel will take the subject's measurements and vital signs and will confirm that the subject meets the Inclusion/ Exclusion criteria.

Sites will make all efforts to maintain a balanced distribution of subjects across the different weeks of pregnancy. An attempt will be made to include at least 5 women with contractions in each site.

5.1.2 Recording session

The primary objective is to assess the agreement between the PregSense™ device data collection, and the values as measured via the standard of care used for prenatal monitoring (i.e. CTG).

First, the authorized study personnel will register the subject into the App. If the subject is already registered, the subject's study I.D number will be entered to the App.

PregSense™ WSB then will be applied by the authorized study personnel to the maternal abdominal area of the subject after cleaning the maternal abdomen with a damp cloth, then drying the abdomen. Before initiating the recording session, a valid signal should be obtained. Therefore, a 2 minutes signal validation test will be executed. If validation test fails, re-adjustment of the PregSense™ WSB connections and placement should be re-validated, then another validation test will follow (if validation test does not pass after three adjustments the subject shall be excluded).

Once the validation test has passed, a 10-minute session will be recorded.

After session completion, the authorized study personnel will apply the CTG transducers, and will confirm fetal heart rate detection according to the standard of care procedure.

If a valid signal is detected, a new 30-minute session will be initiated recording both systems simultaneously in a synchronized method (PregSense™ and CTG).

Following the completion of the sessions, the nurse/clinician will remove both monitoring systems from the maternal abdomen.

5.2 Early Discontinuation

Subjects are free to discontinue their participation in the study at any time and without prejudice to further treatment and without naming the reasons. It will not have any impact on their treatment.

5.2.1 Criteria for Early Discontinuation

Subjects who prematurely discontinue the study should be followed and treated by the investigator in a customary manner.

A subject may withdraw or be withdrawn from the study for the following reasons:

- Subject withdrew consent.
- Request of Sponsor to terminate the study.
- Request of primary care physician or investigator.
- Subject is non-compliant with study procedures.
- Protocol violation.
- Subject is unable to continue the study.
- Subject experiences an adverse event (whether considered related to the investigational product or not) that results in a medical condition that may prevent the subject from meeting study criteria.
- Death.

Reasons for premature withdrawal from the study must be stated in the CRF and in the site source documentation.

If there is more than one reason for early withdrawal from the study, all the reports should be stated.

The study may be stopped following an unexpected event, which does not permit continuation of the study. The Investigator and/or the Sponsor and/or local EC and/or regulatory authority/Competent Authorities can decide to terminate the study.

The data collected up until the withdrawal point will be valid and available for insertion into the study database and the development of the analysis.

5.2.2 Sponsor's Termination of Study

The Sponsor reserves the right to discontinue the study at any time for any reason. The Sponsor may also discontinue the study at a site due to poor performance or compliance. The investigator must implement the Sponsor's request to terminate the study in a time frame that fits best with the subjects' well-being.

6 SUBJECT ELIGIBILITY

6.1 Inclusion criteria:

The study population will consist of the following inclusion criteria:

1. Female age between: 18-50
2. Gestational age >32 + 0 weeks
3. Singleton pregnancy
4. Ability to understand and sign informed consent

6.2 Exclusion criteria

1. BMI ≥45 and 15≤ prior pregnancy
2. Multiple gestation
3. Fetal Anomaly
4. Uncontrolled Hypertension
5. Subjects with skin problems in the abdominal area (such as; wounds, cuts in the skin, skin rash, etc.)
6. Subjects with implanted electronic devices (pacemakers, defibrillator, etc.)
7. Subjects who, in the judgment of the investigator, are likely to be non-compliant or uncooperative during the study

7 STUDY CONDUCT

7.1 Screening & Enrollment

The enrollment procedure will include:

- Assessment of eligibility to participate in the study.
- Informed Consent must be obtained prior to enrollment.
- The subject will undergo routine registration procedure and will be identified by a personal code in addition to their initials.
- The Case Report Form (CRF) will be filled by certified and trained clinician and/or authorized personnel, including recording of all relevant subject details (such as Weight, height, estimated Due date, concomitant medications, medical history, date of signature on the ICF, recording date and hour, problems detected during recordings, etc.).

7.1.1 Assessment of eligibility

Study authorized personnel will evaluate subjects' eligibility to participate in the study. All potential trial candidates will be screened for eligibility. Only subjects who meet all inclusion criteria and none of the exclusion criteria will be eligible for enrollment.

Eligibility to participate in the study will be ascertained by the investigator based on the inclusion and exclusion criteria.

Sites will make all efforts to enroll an equal number of the subjects across the different gestational age.

7.1.2 Informed Consent Process

The subject will be requested by the investigator to sign the ICF, according to the declaration of Helsinki and local regulations. The subject will receive a full oral explanation on the study and will receive a copy of the subject ICF and subject Information Form.

The consent to participate in this study must be given in writing. The signed informed consent will remain in the file of the subject; a signed copy will be given to the subject.

A subject identification log (LOG-CLI-04-04) will be kept at the site with all subjects signed ICF documentation for participating in the study. The log will include the subject's full name, ID number, initials, subject number and date of enrollment.

7.1.3 Subject identification code

Following the enrollment, each subject will be assigned a unique study number that will be used to identify results. The subject will receive an identification number of 10 digits.

The first digit will be the code of the country; "1" for Germany, "2" for USA etc.

The 2nd and 3th digits will be the code of the site; "01" for Heidelberg, "02" for Hadassah etc. the 5th, 6th and 7th digits will be the code of the protocol; "1000" for the Pivotal trial etc. The last 3 digits (8th to 10th digits) will be the code of the subject CRF number; "001, "002" etc.

The identity of all study participants will be kept strictly confidential.

7.2 Recording session

In general, the treatment of a subject enrolled to the study will be performed according to the medical and hospital guidelines. Each recording session will last at least 30 min as according to the standard of care.

Important Note: The physician or any other medical personnel are not allowed to make any medical decisions or treatments based on the information received from PregSense™.

7.2.1 Recording

The PregSense™ will be connected and operated in the most continuous manner as possible recording the fetal cardiac activities and maternal cardiac activities, unless there is a necessity to disconnect the subject due to medical treatment or nursing reasons.

The data will include the following:

- Fetal HR
- Maternal HR
- Uterine activity

The PregSense™ records will be identified by the subject's trial identification number.

7.2.2 CTG and data recording

The data from the CTG + Pulse Oximeter monitoring system will be recorded in real time by a dedicated SW system in parallel to the PregSense™.

A pulse Oximeter is used to monitor MHR with the CTG/NST device.

All data should be stored under the subject study ID number and will be analyzed offline.

7.2.3 Testing Set-up

Additional equipment to be used during the testing:

- CTG - Phillips Avalon FM30/FM20 + Pulse Oximeter with a dedicated PC and cable connections
- Ultra Sound Imaging if applicable

7.3 Standard of Care

During all study periods, subjects will receive Standard of Care in accordance to the general management of the site.

7.4 Concomitant tests, therapy and treatment

All concomitant medications/therapies administered during the study and may affect the data collected are to be recorded in the appropriate CRF page. There are no restrictions on the use of concomitant medications, as dictated by the study device.

Any investigational medication/therapy or off-label uses of drugs and devices are prohibited during the study.

7.5 End of study/Completion of study

Completion of study will be defined by the subject compliance, thus, subjects who finished the study without protocol violations and had at least 1 minute of data where a signal was recorded and detected with both devices at the same time.

8 ASSESSMENT OF SAFETY

PregSense™ is a passive "listening" tool - there is no energy transmitted into the body (unlike ultrasound and Doppler). The sensor communicates with the smartphone/tablet via Bluetooth. Bluetooth is a standard very common, low-energy communication technology.

8.1 Safety parameters

Subjects must be carefully monitored for adverse events. Adverse events should be assessed in terms of their seriousness, intensity, duration, resolution status and relatedness to PregSense™ usage. The outcome of each adverse event must be observed and documented.

8.2 Adverse events

There are no known adverse events related to the use of PregSense™, however, there are possible adverse events related to monitoring systems which involve sensor application on the skin. These include the following:

- Edema
- Erythema
- Irritation
- Sensitization

An adverse event is any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a subject, user or a third person, that appears or worsens during a clinical trial. An adverse event may or may not be related to the investigational device prescribed as part of the trial protocol.

8.2.1 Severity definition:

- Mild: AE which is easily tolerated
- Moderate: AE sufficiently discomforting to interfere with daily activity
- Severe: AE which prevents normal daily activities

The Primary Investigator (PI) will document in his opinion the relationship of the AE to the investigational product (medical device) using the criteria outlined below:

8.2.2 Relationship of an adverse event to the Treatment/ Device

- Unrelated: The AE has no temporal relationship to study device, and/or there is evidence of alternative cause such as concurrent medication or illness.
- Possibly related: A temporal relationship with study device is not clear, alternative causes are also possible.
- Probably related: A clear cut temporal relationship to the use of study device and potential alternative etiology is not apparent.
- Definitely related: A clear cut temporal relationship to the use of study device and no other possible cause.

8.3 Adverse Events (AE) and Severe Adverse Events (SAE) Reporting

The following shall apply to events occurring throughout the trial:

All severe adverse events (SAE) must be reported to the Sponsor within 24 hours after the investigator learns of the event, by faxing/e-mailing the completed Adverse Event Form.

The contact information for reporting to the Sponsor is as follows:

Nuvo Group Ltd.
11th Menachem Begin Rd.
Ramat Gan, Israel
Fax: +972-3-5294072
Email: adar.shani@nuvo-group.com

The sponsor is required to submit a full SAE report as applicable per regulations in each country. A full investigation and report must be submitted by the sponsor to the FDA and to local MOH as applicable, and/or to all reviewing IRBs/EC as soon as possible, but no later than 5 calendar days after the investigator first learns of the unanticipated severe adverse event. Thereafter, the Sponsor must submit any additional reports concerning the event, as FDA/MOH requests.

All other events, including technical failures, will be reported to the Sponsor every monitoring visit, confirmed in writing by the PI and recorded in the Case Report Form

Adverse events occurring in subjects enrolled, user or a third person in the trial must be evaluated and documented in the CRF and will be reviewed by the Sponsor upon every monitoring visit and, as applicable, reported to the Institutional Review Board (IRB) and other appropriate parties per country regulations.

9 STATISTICAL CONSIDERATIONS

9.1 Study Design and objectives

This will be a prospective, comparative, open label, multicenter study with test and reference devices used in each subject. The purpose of this study is to demonstrate safety and performance of PregSense.

9.2 Study Endpoint Measures

9.2.1 Primary Performance Measures

Fetal heart rate (FHR) as measured by PregSense™ versus the standard of care (i.e. CTG).

Maternal heart rate (MHR) as measured by PregSense™ versus the standard of care (i.e. CTG).

Both parameters are measured continuously for a duration of 30 minutes with data sampling taken at 1-minute intervals in parallel with both study devices.

9.2.2 Safety Endpoint Measures

Incidence of device related and/or protocol procedure related adverse events and/or serious adverse events related to the study device, PregSense™, in pregnant women with a singleton pregnancy > 24 +0 gestational weeks.

9.2.3 Secondary Performance Measures

Uterine contractions as measured by PregSense™ versus the standard of care (i.e. CTG including TOCO recordings).

The parameters are measured continuously for a duration of 30 minutes with data sampling taken at 1-minute intervals in parallel with both study devices.

Three blinded assessors will review the recordings and determine for each time point whether a contraction occurred.

9.3 Success Criterion

The study will be deemed successful if the limits of agreement (LOA's) for FHR and MHR between PregSense and the standard of care device are within the interval [-7, 7] Bpm.

In the literature, the limits of agreement for both FHR and MHR with FSE, abdominal fetal ECG and ultrasound were clinically evaluated showing that the abdominal fetal ECG limits of agreement is (± 1.96 SD) 8.40; −8.72[11].

9.4 Sample Size Justification

The company intends to recruit a minimum of 50 subjects for this study. An attempt will be made to include 5 subjects with contractions per site.

The minimum recommended number of measurements for a method comparison study as per EP09-A3: "Measurement Procedure Comparison Bias Estimation Using Patient Samples Approved Guideline – Third Edition") is a sample size of 40 laboratory samples (subjects in our case). The devices will record for 30 minutes with data sampling at 1-minute intervals, i.e. each subject may have up to 30 minutes measurements of FHR and MHR available for analysis, but no less than 1 minute of paired corresponding detection data with both modalities. We expect that on average there will be at least 5 paired measurements per subject. Therefore, if at least 50 subjects are recruited for the study there will be up to 1000 measurements of heart rate with both devices and no less than 250.

[11] http://beijingyes.com/download/Holter_2_Accuracy_and_reliability_of_fetal_heart_rate_monitoring.pdf

In addition, from preliminary company data the mean difference between FHR measurements with two methods was 0.695BPM (SD= 1.15BPM), using the sample size equation from Lu MJ, Zhong WH, Liu YX, Miao HZ, Li YC, Ji MH (2016) Sample size for assessing agreement between two methods of measurement by Bland-Altman method. The International Journal of Biostatistics 12: issue 2 (pp. 8), we find that with a sample size of at least 50 subjects the acceptance criterion can be met at a 5% level of significance and with 90% power even if the standard deviation is almost twice as high as seen in the feasibility study.

An acceptable outcome for the secondary performance measure of Uterine contractions agreement is 85%, in order to estimate this parameter with a two-sided 95% exact binomial confidence interval having a half-width of ±10% at least 65 contractions are required. If each subject experience at least 2 contractions and the within subject correlation is moderate (r=0.5) then a sample size of 44 women will be sufficient to measure this endpoint with acceptable reliability.

9.5 Data Analysis Sets

Full Analysis Set / Safety Analysis Set (SA)

The safety analysis (SA) set includes all subjects who were enrolled and underwent study procedures in with data available for analysis.

9.5.1 Performance Analysis Set (PA)

Because each monitoring modality sometimes fails to generate clinically interpretable data, rules were applied to facilitate statistical analysis.

The performance analysis set will consist of all subjects who finished the study without major protocol violations and had at least 1 minute of data where a signal was recorded and detected with both devices at the same time. Possible reasons for exclusion of a data point from this analysis set may include but are not limited to the following:

Invalid signal in one of the systems, i.e PregSense™ and the CTG system due to:

1. Device malfunction
2. Maternal movement
3. Device positioning does not enable signal recording
4. Interaction between devices

9.5.2 Statistical Analysis of Analysis Sets

The SA set will serve as the analysis set safety assessments. The performance assessments will be performed on the PA set.

9.6 Statistical Analysis

9.6.1 General Considerations

Statistical analyses will be performed using SAS® v9.4 or higher (SAS Institute, Cary NC, USA). Statistical analyses and reporting will be performed in compliance with FDA Guidance E6 GCP and E9 and ISO 14155.

Baseline demographic together with safety analyses will be performed on all subjects if the SA set. Baseline values are defined as the last valid value prior to study device use.

If statistical tests are performed, nominal p-values will be presented. All statistical tests will be two-sided. Where confidence limits are appropriate, a two-sided 95% confidence interval will be constructed.

For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test will be used as appropriate. For comparison of proportions (categorical variables), the Chi-squared test or Fisher's exact test will be used as appropriate.

If multiple measurements are taken in a single subject, statistics will be appropriately modified to accommodate the within subject correlation.

9.6.2 Demographic and other baseline variables

Demographic and baseline pregnancy related characteristics will be tabulated. Continuous variables such as age and BMI will be summarized by a mean, standard deviation, minimum, median and maximum, and categorical variables by a count and percentage.

9.6.3 Disposition of subjects

Subject disposition will be tabulated; the number of enrolled, exposed to study device, prematurely terminated and completed as planned subjects will be summarized, including the number of subjects in each analysis population. Device tolerability and compliance will be presented, the number and percent of subjects who fail to complete the study and the number and percent of subjects who fail to complete the study because of adverse events will be presented. A list of discontinued subjects, protocol deviations, and subjects excluded from the performance analyses will also be provided.

9.6.4 Performance analysis

9.6.4.1 Primary performance:

Fetal heart rate (FHR) and maternal heart rate (MHR) will both be analyzed in a similar manner as follows:

A comparison between PregSense™ measurement of FHR and MHR versus the reference measurements (i.e. CTG) are made using methods described by Bland and Altman[12].

The correlation (Pearson's correlation coefficient) and mean difference between the reference and PregSense™ measures of FHR and MHR will be presented together with a 95% confidence interval. A high correlation and a mean difference value near zero are expected if the two devices (Reference vs. PregSense™) output the same values.

In addition, a Bland-Altman plot of the mean versus the difference will be presented, and the 95% limits of agreement calculated together with respective confidence intervals. As a measure of accuracy, the mean bias and its standard deviation (with 95% confidence intervals) are estimated from random effects analysis of variance models programmed in SAS® using the MIXED procedure. This is done to accommodate the within subject correlation due to repeated FHR and MHR measurements.

Linear regression models (Deming or Passing-Bablok regression as appropriate) will be fitted to the values obtained from both devices of FHR and MHR; the slope and intercept together with respective 95% CI 's will be presented. The confidence intervals of the regression parameters will be calculated with bootstrap methodology using 10,000 simulated samples as well.

9.6.4.2 Secondary performance:

Uterine contractions as measured by PregSense™ and the standard of care (i.e. CTG including TOCO recordings), are measured continuously for a duration of 30 minutes with data sampling taken at 1-minute intervals in parallel with both study devices. We shall count the number of contractions (may be more than one per subject) as determined by the blinded assessors at each time point for which there was agreement between the PregSense™ and the standard of care. The percent of agreement (i.e. positive agreement) will be presented, the denominator of this fraction will be the standard of care number of identified contractions per subject. The binary positive agreement variable will be modeled with a

[12] https://en.wikipedia.org/wiki/Bland%E2%80%93Altman_plot

repeated measures model for binary data using the GENMOD procedure in SAS (link=identity dist=bin). This is done to accommodate the within subject correlation due to repeated measurements. The intercept of the model is the parameter of interest; this will be presented with corresponding 95% confidence interval. A point estimate for the agreement that is considered acceptable is 85%. Note that if the agreement will be 100% a Wilson score confidence interval will be presented instead.

The false positive alert rate will be analyzed in a similar manner. At each time point, no notation of a contraction by each of the modalities will be considered negative for uterine contraction, therefore the false positive alert rate will count the number of falsely identified contractions by the PregSense™ relative to the SOC.

9.6.4.3 Safety Analysis

Adverse events (AE) will be presented by seriousness, severity and relation to study device. The primary safety variable, the cumulative incidence (and 95% CI) of device-related adverse events (AEs) and SAE's observed throughout the follow-up period, will be presented in a tabular format. A detailed list of all adverse events will be presented. The adverse event rate will be compiled with respect to frequency, nature, severity of the event, and relationship to the study device. In addition, listings of all safety measures will be provided.

The rate of SAE's, if any, associated with use of PregSense™ is expected to be very small.

9.6.5 Pooling

Poolability of the study centers will be evaluated by comparing the demographic and baseline parameters between the centers by data type. If the differences between the centers are found significant, the reasons for these differences will be further explored and rationalized with reference to the effect on the main performance parameters.

9.6.6 Handling of missing data

No imputation of missing values will be performed. Each subject is expected to contribute at least one data point to the analysis of the primary endpoint, therefore only missing data points will be excluded from the analysis of the relevant endpoint.

10 STUDY MONITORING & QUALITY ASSURANCE AUDITS / INSPECTIONS

10.1 Good Clinical Practice

The study described in this protocol will be carried out according to the local regulatory requirements (FDA, EU) and ICH accepted standards of Good Clinical Practice. All procedures not described in this protocol will be performed according to the approved written Standard Operating Procedures unless otherwise stated.

10.2 Monitoring Procedures

The Study Monitor will be responsible for ensuring adherence to FDA, EU Directives, ICH guidelines and the Sponsor's Standard Operating Procedures.

Experienced independent monitors or monitors from CROs/Sponsor will be trained in the Sponsor's SOPs, study protocol and the study monitoring conventions.

Regular monitoring of study data at each site will be performed as defined by the study specific monitoring plan. Individual sites will be monitored to verify that enrollment rate, data recording, and protocol adherence are satisfactory. The frequency of monitoring individual sites may fluctuate depending upon enrollment rate, quantity of data collected and the complexity of the study and will be described in the monitoring plan.

These monitoring visits will be performed for the purposes of verifying adherence to the protocol and the completeness and accuracy of data entered on the CRF. The study monitor will verify CRF entries by comparing them with the primary source documents (hospital/clinic/office records), which will be made available for this purpose. The monitor will review the maintenance of regulatory documentation and device accountability. The monitor will review the progress of the study with the investigator and other site personnel on a regular basis. At the end of the study, a close-out monitoring visit will be performed. Monitoring visits will be arranged in advance with site personnel at a mutually acceptable time. Sufficient time must be allowed by the site personnel for the monitor to review CRFs and relevant source documents. The coordinator and/or investigator should be available to answer questions or resolve data clarifications.

10.3 Quality Assurance Program

This clinical trial may be audited according to the Nuvo Group Quality Assurance (QA) program/Nuvo-Group designee.

The purpose of these audits is to determine whether the study is being conducted and monitored in compliance with the protocol as well as recognized GCP guidelines and regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a subsequent inspection by any regulatory authority. Such audits, if necessary, will be pre-arranged with the site and conducted within a reasonable time frame.

10.4 Regulatory Inspections

The study may be inspected by regulatory agencies. These inspections may take place at any time during or after the study and are based on the national regulations, as well as ICH guidelines.

11 USE OF INFORMATION AND PUBLICATION

11.1 Confidential Information

All information supplied by Nuvo Group in connection with this study and not previously published in the public domain, is considered confidential information. This information includes, but is not limited to, the Investigators' Brochure, clinical protocol, case report forms and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of Nuvo Group, shall not be disclosed to others without the written consent of Nuvo Group, and shall not be used except in the performance of this study.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Nuvo Group in connection with the development of the device. The information may be disclosed as deemed necessary by Nuvo Group. To allow the use of the information derived from this clinical study, the investigator is obliged to provide Nuvo Group with complete test results and all data developed in this study. The information obtained during this study may be made available to other investigators who are conducting similar studies.

Should the investigator wish to publish the results of this study, the investigator agrees to act according to Nuvo Group Publication policy.

12 ETHICAL AND LEGAL ASPECTS

12.1 Compliance with Regulations Applicable to Clinical Trials

The study will be conducted according to the laws, regulations and administrative provisions relating to the implementation of Good Clinical Practice in the conduct of clinical trials, as applicable by national

legislation and EU Directives, including 93/42/EEC, 90/385/EEC, ISO 14155and US 21 CFR Part 812 and local regulations where applicable.

12.2 Informed Consent

The principles of Informed Consent, according to Declaration of Helsinki 1964 and all its updates, ICH guidelines on GCP, 21 CFR part 50 of the FDA Regulations and/or EU Medical Devices Directives 93/42/EEC, 90/385/EEC and ISO 14155, will be followed. A subject should not enter a clinical study until he/she has been properly informed, has been given time to contemplate participation, and has freely given his/her consent by signing and dating the EC/IRB approved informed consent form. This must be done prior to performing any study related procedures.

The proposed consent form and any other documents relevant to the consent process, must be submitted to the Ethics Committee/Institutional Review Board (EC/IRB), together with the protocol, and must be approved prior to study start.

A copy of the fully signed and dated Informed Consent and any other documents relevant to the consent process will be given to the subject and the original will be maintained at the site.

12.3 Ethics Committee (EC) / Institutional Review Board (IRB)

The study must have unconditional approval in writing, by an appropriate Ethics Committee/Institutional Review Board (EC/IRB). A copy of the Letter of Approval from the EC/IRB, which contains specific identification of the documents approved, must be received by Nuvo Group 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 investigator brochure that is approved by Nuvo Group, must also be approved, as appropriate, by the EC/IRB and documentation of this approval provided to Nuvo Group. Records of the EC/IRB review and approval of all documents pertaining to this study must be kept on file by the investigator and are subject to regulatory authority and/or sponsor inspection during or after completion of the study.

Serious/ unanticipated adverse events (SAEs) must also be reported to the EC/IRB by the Investigator or the Sponsor.

Periodic status reports must be submitted to the EC/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 EC/IRB must be sent to the sponsor.

12.4 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 EC/IRB prior to implementation.

12.5 Subject Confidentiality

All subject data will be identified only by a subject identification number and date of birth.

After obtaining 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. This shall include all study relevant documentation including subject medical history to verify eligibility, laboratory test result reports, admission/discharge summaries for hospital admissions occurring while the subject is on study, and autopsy reports for deaths occurring during the study (where available).

Subject authorization must allow Nuvo Group to receive and review the subject's protected health information which may be re-disclosed to any authorized representative of Nuvo Group, Central

Reading Facility or central laboratory facility for review of subject medical records in the context of the study.

12.6 Insurance

All subjects participating in the study will be covered by the insurance issues by the Sponsor in accordance with applicable local laws.

The insurance certificate will be provided as part of the submission package to the local ethical committee and MOH as applicable.

13 DOCUMENTATION

13.1 Study File and Site Documentation

Prior to the initiation of the study, the following items must be received by the Sponsor from the site:

- Confidential Non-Disclosure Agreement
- Signed protocol, amendments and notifications pages
- The Principal Investigator's curriculum vitae and where required current medical license
- Signed Clinical Study Agreement and Signed Investigator Agreement
- EC/IRB written approval for the Protocol, Amendments, Informed Consent, Subject Information Sheet
- EC/IRB Membership list or an official statement from the EC/IRB stating the they are in compliance with 21 CFR part 56
- Financial disclosure information on possible conflicts from all investigators

13.2 Study Documentation Supplied by the Sponsor

The Sponsor/ CRO will supply the investigator with the following items:

- Case Report Forms (CRF)
- Regulatory Binder
- Template Informed Consent
- Valid Insurance Certificate
- Operations Manual

13.3 Preliminary Source Documents

The investigator must maintain primary source documents to support CRF data entries. These documents, which are considered "source data", may include but are not limited to:

- Demographic information
- Ultrasound results (if applicable)
- Evidence supporting the diagnosis/condition for which the subject is being studied
- General information supporting the subject's participation in the study
- Medical history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Any relevant findings/notes by the investigator(s), occurrence (or lack) of adverse events, and changes in medication usage, including the date the study medication was commenced and completed
- Original, signed informed consent forms for study participation

The investigator must also retain all subject specific printouts/reports of tests/procedures performed as a requirement of the study. During monitoring visits, the monitor will need to verify data in the CRFs against these source data.

13.4 Additional Documents and Records

- Subject Screening and Assignment Log – A listing of all subjects who signed the informed consent and were screened.
- Subject Identification Record - This allows linking of the enrolled subject to the study. Information should include, but is not limited to: subjects' name, date of birth and contact information. This confidential list will be maintained by the investigational site and should not be forwarded to the Sponsor.
- Device Inventory/Shipment Form – This form documents the total amount of devices shipped to the site and received and acknowledged by the investigator, or designee.
- Device Accountability Log – This form documents the total amount of study device dispensed to and returned by each subject.

13.5 Maintenance and Retention of Records

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

- A period of at least two years from last marketing authorization and notification from sponsor
- A period of at least two years after discontinuation of clinical development of the investigational product as confirmed by Nuvo Group
- Longer, if required by local regulations

The investigator will be instructed to consult with Nuvo Group before disposal of any study records and to provide written notification to Nuvo Group of any change in the location, disposition, or custody of the study files.

14 INVESTIGATIONAL PRODUCT

All investigational devices will be provided to the clinical sites by Nuvo Group, and Nuvo Group will be responsible for device servicing and replacement. All failures and malfunctions will be reported to Nuvo Group within 24 hours via e-mail to: Adar.shani@nuvo-group.com.

14.1 Supply and Disposition of Study Devices

An adequate number of PregSense™ will be supplied to the study sites before initiating the study.

Upon completion of trial, the devices will be returned to the Sponsor to avoid unauthorized use.

Each shipment of device supplies for the study will contain a shipment form to assist in maintaining current and accurate inventory records. When a shipment is received, the investigator/coordinator will acknowledge receipt.

14.2 Device Accountability

Accountability records must be maintained at the site at all times. The identification number of the subject, the date, lot number, expiry date of the Sensor dispensed, and the date and quantity of devices returned will be recorded. The devices will be noted on the appropriate inventory forms.

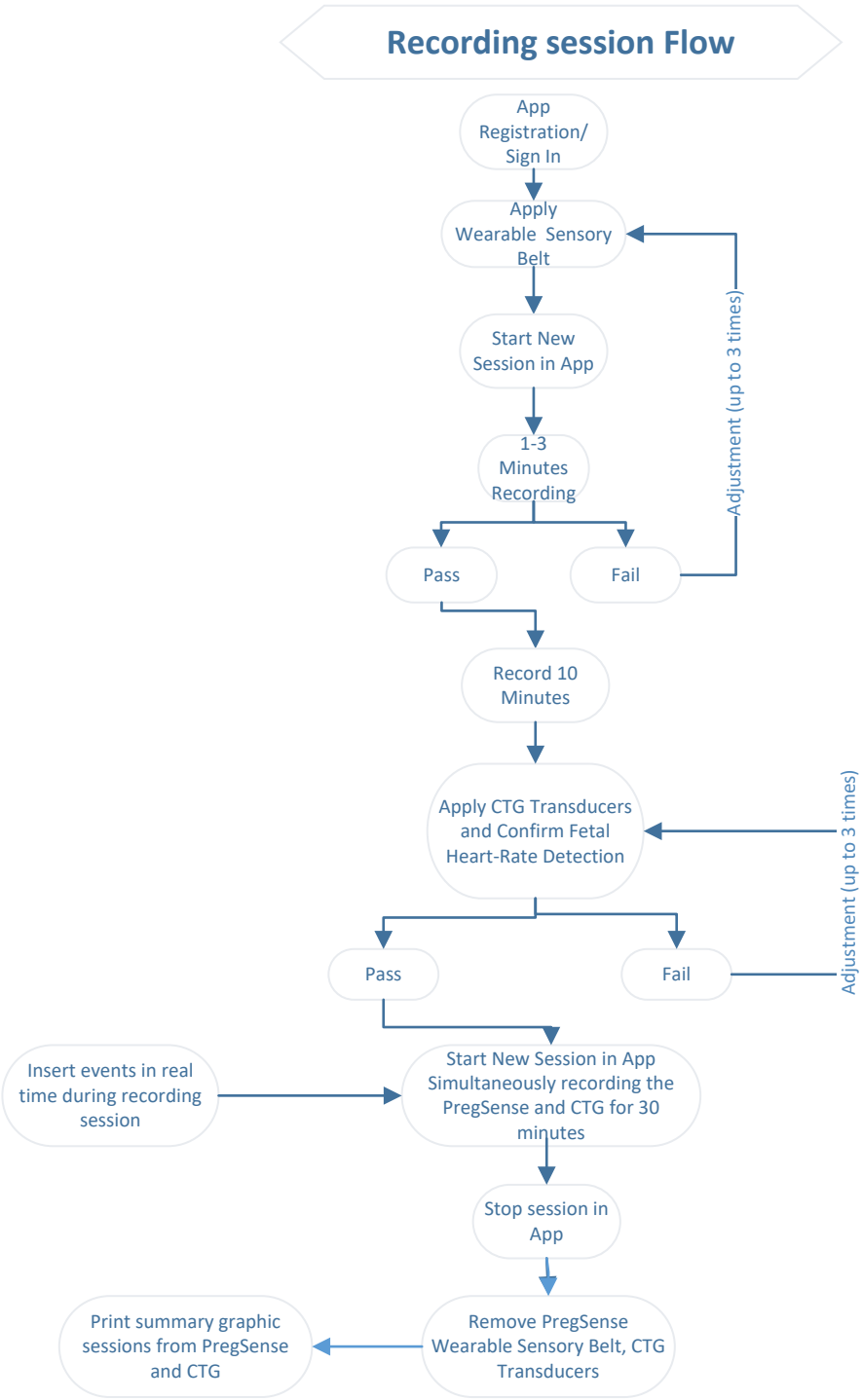
At study conclusion, all devices must be returned to the sponsor or sponsor's designee. Ancillary supplies may not have to be returned.

Upon Nuvo Group/Nuvo Group designee visit at the site, accountability of the returned devices should be performed and recorded.

15 APPENDICES

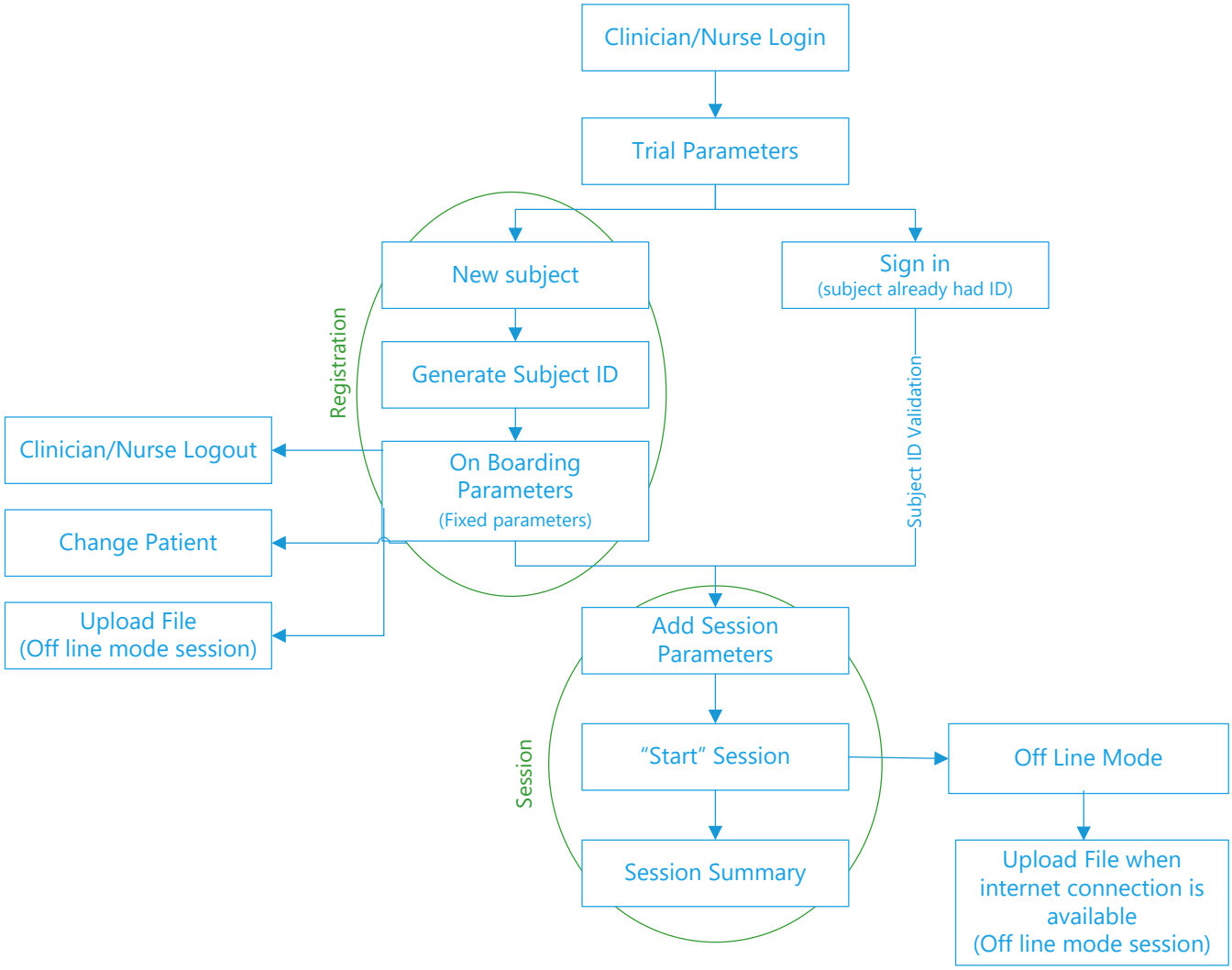
15.1 Appendix 1 –Recording Session Flow

Figure 8 Recording Session Flow



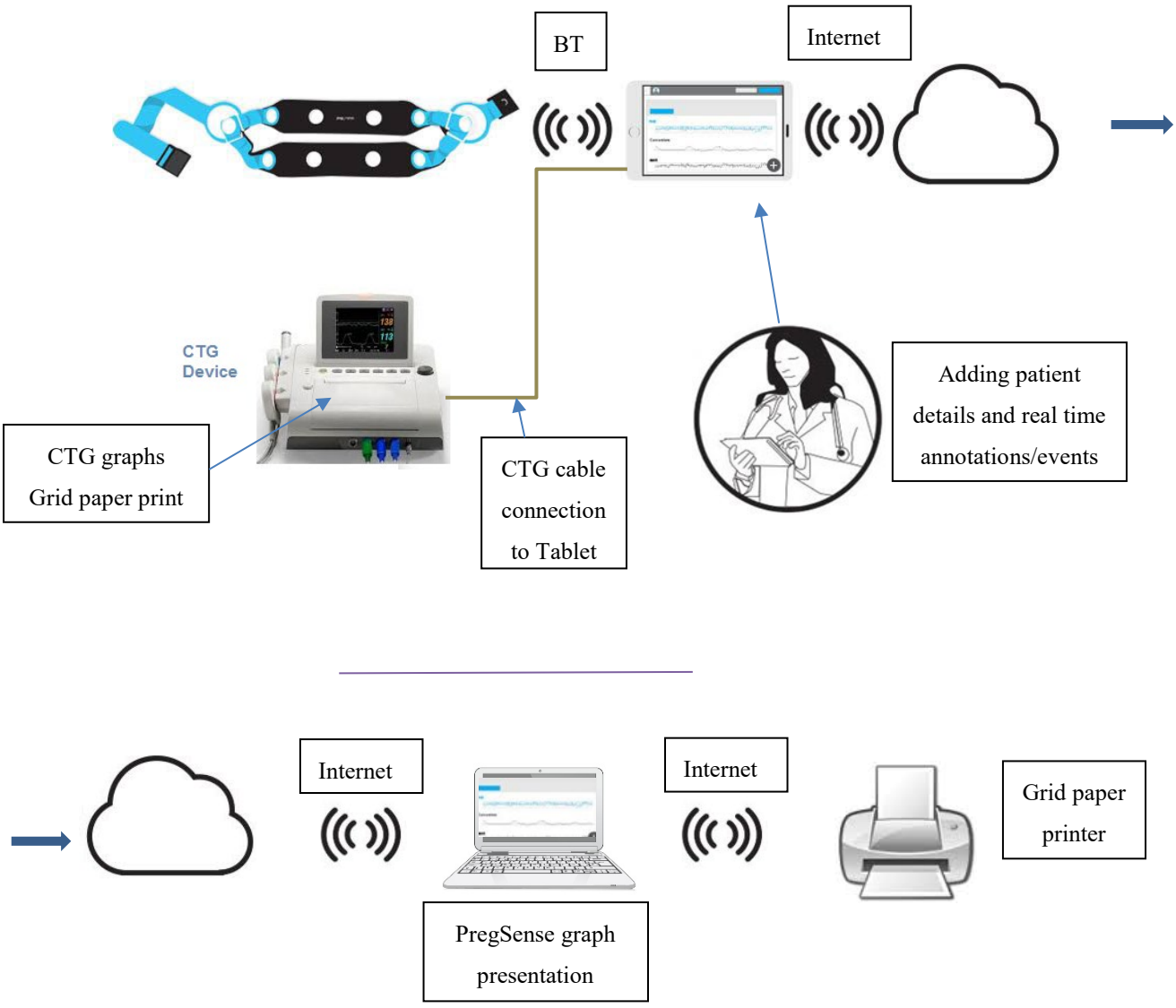
15.2 Appendix 2 – Pivotal study Application Flow

Figure 9 Pivotal study Application Flow



15.3 Appendix 3 – Pivotal Study Setup Flow

Figure 10 Pivotal Clinical Trial Setup Flow:



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