RESEARCH PROTOCOL (nWMO)

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PROTOCOL TITLE Development of an international remote digital care system for accessible, inclusive and sustainable pregnancy care

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1. INTRODUCTION AND RATIONALE

The incidence of medical pregnancy care is rising in the Netherlands. Between 1999-2012, 34% of women gave birth in primary care [1], while only 24% of women did so in 2020 [2]. This rising need for medical care coincides with growing shortages in obstetric healthcare professionals (OHPs) and growing costs. Increasing demand and decreasing supply may result in substandard care, affecting pregnant women in vulnerable circumstances the most. Thus, there is an urgent need to innovate current medical pregnancy care and move care from hospital to home when possible. MedTech innovations for remote digital pregnancy care (RDPC) are available.

In recent years, the MedTech industry developed various blood pressure measuring devices to monitor maternal blood pressure (MBP) from home, as well as cardiotocography (CTG) devices capable of monitoring fetal heart rate (FHR) from home thus enabling remote digital pregnancy care (RDPC). These developments include the development of data platforms connecting remote devices to the Electronic Medical Record (EMR).

In the past decade we have performed pioneering research of RDPC point solutions for the monitoring of pregnancy complications. In the randomised HoTel trial (PI Mireille Bekker, UMC Utrecht METC nr. 16-516), home-monitoring of fetal heart rate, maternal symptoms, and blood pressure was feasible and as safe as in-hospital admission in complicated pregnancies, with lower costs and better end-user experience [4].

RDPC is ready for the next level, but its wide-scale use is hampered by lack of knowledge on the impact on health equity, reimbursement and cost-effectiveness, and lack of key enabling methodologies including digital care paths, change models, and a FAIR data infrastructure to embed RDPC in care paths, the electronic medical record (EMR) and payment models. Although ‘point solutions’ are available, both the MedTech and healthcare sectors need innovative ‘system solutions’ to overcome these knowledge and methodology gaps together and work towards large-scale application of RDPC.

PregnaDigit/PREGmatic will expand on this state-of-the-art by developing and evaluating a ‘system solution’ that addresses all forementioned knowledge and methodology gaps hampering RDPC upscaling. By industrial and experimental research we will design care paths and solutions for health inequities, costing and a FAIR data infrastructure with prediction models. The project will deliver knowledge, insights, recommendations, business models and roadmaps for market entrance. PregnaDigit/PREGmatic will thus facilitate nationwide and international adoption of RDPC as the new standard of care.

PregnaDigit/PREGmatic's system solution aims to keep pregnancy care accessible for all women, regardless of their socioeconomic status, and relieve pressure on the health system while reducing costs. We aim to enable the hybrid transformation and care replacement of a substantial part of current pregnancy care to RDPC by 2030.

2. OBJECTIVES

Primary Objective: to facilitate nationwide and international adoption of RDPC as the new standard of care.

Secondary Objective(s): our objectives are described in the following work packages (WP):

WP	**Objective(s)**
1 Management and strategy	Overall PregnaDigit EU/PREGmatic Management & Strategy.
2 Change & Care models	Implement and evaluate care models incorporating RDPC for high-risk pregnancies in four academic hospitals.
3 Cost & Reimbursements	Measure differences in costs between current care and new care with incorporated RDPC. Design alternative payment models for RDPC.
4 Medtech and Technology	Evaluate end-user experiences regarding CTG devices and their patient- and clinician dashboarding and platform solutions. Determine usability and scalability for a wider range of pregnancy complications and digital connection to end-users
5 Data support	Set up FAIR data structure which will make data supported decision making and benchmarking available to prove our Value Case of RDPC.

3. STUDY DESIGN

A prospective cohort study with a retrospective control group will be conducted. The duration of the intended first part of the study is 12 months. This study will be conducted in the UMC Utrecht, Karolinksa University hospital and Vall d'Hebron hospital. The duration of the second part of the study is 36 months. This study, a continuum of part 1, will be conducted in

the UMC Utrecht, the Erasmus Medical Center, Karolinska University hospital and Aarhus University hospital.

4. STUDY POPULATION

4.1 Population

Pregnant women with manifest complications, such as hypertensive disorders of pregnancy, fetal growth restriction, premature rupture of membranes, decreased fetal movements, and a perinatal death in a previous pregnancy. According to consensus guidelines, these women require hospital admission for fetal and maternal monitoring. In PregnaDigit/PREGmatic however these women will be monitored at home by RDPC in a new care model using CTG & MBP devices, and online platforms. These women comprise an estimated 10% of the pregnant population. In the Netherlands, patients requiring CTG home monitoring who are enrolled from the Erasmus Medical Center or University Medical Center Utrecht will be included in both the PregnaDigit EU study and the PregnaDigit NL study (OBS_24U-1334) during the duration of the EU study.

4.2 Inclusion criteria

- Gestational age ≥26 weeks
- Age ≥18 years
- Singleton pregnancy
- The presence of one (or more) of the following complications according to local protocol requiring CTG monitoring:
    - Pre-eclampsia*
    - Preterm rupture of membranes
    - Fetal growth restriction**
    - Recurrent reduced fetal movements
    - Fetal anomaly requiring CTG monitoring
    - Intra-uterine fetal death in a previous pregnancy
    - Other reasons requiring CTG monitoring
- Ability to understand Dutch, English, Spanish, Swedish or Danish
- Ability to provide written informed consent
- Ability to understand study instructions

*Preeclampsia is gestational hypertension accompanied by ≥1 of the following new-onset conditions at or after 20 weeks' gestation:

- Proteinuria
- Other maternal organ dysfunction, including:
    - Acute kidney injury (creatinine ≥90umol/L; 1 mg/dL)
    - Liver involvement (elevated transaminases, eg, alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric abdominal pain
    - Neurological complications (examples include eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata)
    - Hematological complications (thrombocytopenia–platelet count <150 000/μL, disseminated intravascular coagulation, hemolysis)
    - Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth)

** For example, FGR is defined as:

- Fetal abdominal circumference (FAC) or estimated fetal weight (EFW) <10th percentile and abnormal Doppler sonography assessment defined as pulsatility index of umbilical artery >p95 and/or absence or reversed enddiastolic flow velocity flow of umbilical artery
- FAC or EFW <p3 with or without abnormal umbilical artery Doppler flow

4.3 Exclusion criteria

- Pregnancy complications requiring IV therapeutics
- Pregnancy complications with requiring an (expected) obstetric intervention within 48 hours
- Current blood pressure ≥160 mmHg systolic or ≥110 mmHg diastolic
- Active antepartum haemorrhage
- CTG with abnormalities indicating fetal distress or hypoxia
- Place of residence >30 minutes distance from a hospital
- Implanted medical device (e.g. pacemaker)

4.4 Sample size calculation

Since our main objective is to facilitate nationwide and international adoption of RDPC as the new standard of care, a sample size calculation is not indicated. Based however on our

experience in the HoTeL study (METC nr. 20-442) [3], we expect to include a total of 400 patients internationally.

5. INVESTIGATIONAL PRODUCT / MEDICAL DEVICE

Remote CTG monitoring will be performed by ICT HCTS and Nemo, both CE certified CTG devices. In this study, the devices are *not* an investigational product.

6. METHODS

6.1.1 main study parameter

Implementation

The implementation process of home monitoring will be analyzed according to the taxonomy of Proctor et al [8].

Proctor defined 8 implementation outcomes: acceptability, adoption, appropriateness, feasibility, fidelity, costs, penetration and sustainability (appendix table 1). These outcomes form the main study parameters for assessment of the implementation of home monitoring in PregnaDigit/PREGmatic:

- Acceptability: the perception among patients and obstetric healthcare professionals that home monitoring is agreeable, palatable, or satisfactory
- Adoption: the initial decision to implement home monitoring
- Appropriateness: the perceived fit, relevance, or compatibility of home monitoring for all
    - stakeholders
    - achievement of specific benefits: enhancing patient autonomy, improved quality of life due to reduced hospital visits, increased patient independence and self-esteem, increased patient satisfaction and compliance
- Feasibility: the extent to which home monitoring can be successfully used or carried out within the hospital
- Fidelity: the degree to which home monitoring was implemented as it was described in the original protocol
- Costs: financial impact of the implementation of home monitoring. May include costs of treatment delivery, cost of the implementation strategy, and cost of using the service setting
- Penetration: the integration of home monitoring in a hospital

- Sustainability: the extent to which the use of home monitoring is maintained within a hospital

Clinical effectiveness

In order to assess clinical effectiveness we will measure a composite outcome of perinatal mortality and maternal and neonatal morbidity.

The composite of perinatal outcome is defined as:

- perinatal mortality (maternal or fetal/neonatal),
- a 5-minute Apgar score below 7 and/or an arterial cord blood pH below 7,05,
- maternal morbidity (one or more of the following:
    - pre-eclampsia (defined according to section 4.3), eclampsia (new-onset, generalized, tonic clonic seizures or coma in woman with preeclampsia), HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count probably representing a severe form of preeclampsia), venous thromboembolic events (deep vein thrombosis and/or pulmonary embolism)
- NICU admission of the new-born and during-labor caesarean section

6.1.2 Secondary study parameters

Management & Strategy

Aim	Overall PregnaDigit EU Management & Strategy
Description & tasks	The Central Management Team (CMT) consists of EUR and the UMCU. The CMT will ensure that the overall PregnaDigit EU/PREGmatic objectives are met and thus leads ongoing co-creation, planning, strategy, communication, and training. The CMT meets weekly. The academic hospitals, MedTech & technology partners will ensure local adoption of the new care models, IT connections with the new devices, possibly within the existing EMRs, and data sharing for both the benchmarking on outcomes, clinical time, processes and experiences. After the initial local set-up phase, they will meet monthly. The PregnaDigit EU/PREGmatic Consortium includes all PregnaPartners. Every 6 months an internal update and evaluation meeting on planning and strategy for all work packages and patient representative organizations will be held towards the final delivery of the manual and roadmap.

Change & care models

Aim	Implement and evaluate care models incorporating RDPC for high-risk pregnancies four academic hospitals. Develop a the RDPC system solution and focus on hybrid care path implementation and usage of these care models taking change behaviour and views of all end-users into account.
Description	**Task 2.1 [New care models for RDPC]** 2.1.1. Implement care models in a multidisciplinary setting with participating obstetric care professionals and end-users, facilitating and embedding RDPC for high-risk pregnancies replacing the in-hospital care monitoring. Population and intervention: Pregnant women with manifest complications, such as hypertensive disorders of pregnancy, fetal growth restriction, premature rupture of membranes, decreased fetal movements, and a perinatal death in a previous pregnancy. According to consensus guidelines, these women require hospital admission for fetal and maternal monitoring. In PregnaDigit EUPREGmatic these women will be monitored at home by RDPC in a new care model. 2.1.2 Draw up Metro maps of the care as usual and the new care pathways to clarify the difference in care activities and costs. 2.1.3 Measurement of clinical outcomes and user experiences with trained end-users. We will measure maternal and neonatal mortality and morbidity, and patient-reported health (ICHOM) and quality of life status, next to experience measures for both patients and clinicians. We will also measure process indicators such as inpatient admission days, days of telemonitoring, and amount of clinician contact. **Task 2.2 [Develop a RDPC transformation manual]**

	2.2 Develop a system manual that enables European upscaling of RDPC. We will perform a stakeholder analysis with all stakeholders (including professionals, end-users, payors) according to the taxonomy of Proctor et al. using semi-structured interviews and questionnaires (based on NOMAD and MIDI validated questionnaires).
Deliverables	D2.1.1 RDPC care models available D2.1.2 Metro maps of care models D2.1.3 Insights in clinical outcomes and user experiences of RDPC D2.2 Launch of RDPC transformation manual

Costs & reimbursements

Aim	To measure the actual differences in cost between the current care and the new care with incorporated RDPC. To design an alternative payment model for the systemic and integrated use of home monitoring tools in healthcare.
Description	3.1 Measuring cost of care as usual and new care (09-2024 - 12-2025) Measure costs of care-as-usual and new RDPC using Metro maps developed in WP2. 3.2 Budget impact analysis (01-2025 - 09-2025) Evaluate where can we see savings and whether they extrapolate to new reimbursement possibilities. 3.3 Alternative payment models (09-2025 – 12-2025) Together with payors, propose new payment models fitting the systemic change (for example, by using shared savings) and conduct a retrospective analysis of changes in reimbursement and costs.
Milestones	3.1.1 Costs of care-as-usual [12-2024] M3.1.2. Costs of new care RDPC [12-2025] M3.2 Budget impact analysis [09-2025] M3.3 Payment models fitting the new care [12-2025]

MedTech & Technology

Aim	Evaluate end-user experiences regarding CTG devices and their patient- and clinician dashboarding and platform solutions. Determine usability and scalability for a wider range of pregnancy complications and digital connection to end-users.
Description & tasks	4.1 Evaluation of instalment and usage experiences (09-2024- 10-2025).We will assess the experiences of pregnant women and health care professionals through interviews and questionnaires identifying barriers and successes during IT connectivity and usage. 4.2 Development of a user-guideline for implementing new medical devices in a remote care setting. (10-2025 - 12-2025). We will develop a user-guideline and requirement/specification documentation for using such CTG medical devices in hospital care.
Milestones	M4.1 User experiences of pregnant women and health care Professionals [10-2025] M4.2 Requirements and specifications [12-2025]

Data Support

Aim	Set up FAIR data structure which will make data supported decision making and benchmarking available to prove our Value Case of RDPC.
Description & tasks	Preparation of the total measurement set including coding and data collection (case report forms and data infrastructure) ready upon start of patient inclusion in January 2025. Ready for data-extractions and analysis on a 6-monthly base.

6.2 Other study parameters

Find the parameters needed to complete the above mentioned deliverables in the attached excel sheet “Core_dataset_PregnaDigitEU_05112024”.

6.3 Study procedures

When one of the prespecified indications for fetal monitoring (see 4.2) occurs, this will be executed via telemonitoring. Patients are instructed to send a CTG once daily using one of the available devices. The CTG will be sent to the hospital via a platform, either stand-alone, or integrated in the electronic medical record depending on the device used. The CTG will be

assessed by obstetric health care personnel (e.g. midwife, gynaecologist, resident) the same day. Maternal parameters, such as temperature or blood pressure are measured daily by the patient if indicated.
If it is necessary for the participant for either maternal or fetal indication to be admitted to the hospital ward or labor ward, all data of interest during the admittance will be collected. If it is possible for this same patient to be discharged again, she will go home with telemonitoring and we will still follow this patient during prenatal care and delivery.
Both patients and obstetric healthcare providers will be invited to complete an online questionnaire, distributed via Castor EDC, to gather data on their experiences with CTG home monitoring. These questionnaires are designed to facilitate an analysis of the primary outcomes, specifically focusing on implementation outcomes.

6.4 Withdrawal if individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

6.5 Replacement if individual subject after withdrawal

NA

6.6 Follow-up of subjects withdrawn from treatment

Subject having withdrawn from the study will be offered care as usual.

7. 7. STATISTICAL ANALYSIS

For the primary analysis of implementation, the scores of the implementation questionnaire filled out by one time by patients and by the obstetric healthcare providers at baseline and halfway the study will be compared. The paired t-test will be used if the outcome is normally distributed and a non-parametric Wilcoxon signed-rank if skewed. These outcomes will be presented as means with standard deviation, geometric means with 95% CI, or as median with interquartile range, whichever appropriate. To evaluate determinants for success and failure of implementation, our primary outcome will be further analyzed for contributing factors using a regression model.

The secondary outcome is the clinical effectiveness. The composite (dichotomous) endpoint of perinatal mortality, a 5-minute Apgar score below 7 and/or an arterial pH below 7,05, maternal morbidity (such as eclampsia, HELLP syndrome, thromboembolic events), NICU admission of the newborn, will be analyzed with logistic regression analysis with correction of predefined confounders as parity and diagnosis of pregnancy complication.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

The study will be conducted in the Netherlands according to ‘gedragscode gezondheidsonderzoek’ and in all (inter)national sites in accordance with the EU GDPR (General Data Protection Regulation) and other (local) guidelines, (local) regulations and (local) Acts (e.g. in the Netherlands the WGBO (Wet geneeskundige behandelingsovereenkomst).

8.2 Recruitment and consent

Pregnant women included in the Pregnadigit EU/PREGmatic study from the Netherlands, both in the retrospective and prospective cohorts, specifically from the Erasmus Medical Center and the University Medical Center Utrecht, are recruited and asked to provide informed consent in accordance with the study protocol patient information leaflet and informed consent form from the Pregnadigit NL protocol (OBS_24U-1334). Pregnant women recruited from European partner hospitals will be asked to provide informed consent following the local guidelines and regulations.

9. ADMINISTRATIVE ASPECTS

9.1 Handling and storage of data and documents

Data will be collected in a web-based registry (Castor EDC). This is a ‘good clinical practice’ classified online data management system. Data collection and entry will be done by the local research team. Data will be managed according to the datamanagementplan (ID 159476). The datamanagementplan is set up in agreement with the datamanager of the division of Woman and Baby. Participants will be given a computer generated numeric code. The code consist of a centre number plus a random number. The key to decode study subjects will only be available to the local coordinating investigator. Persons who have access to the data include: local research staff and local monitoring & quality assurance personnel. The data will be kept for 10 years. The handling of personal data complies with the European General Data Protection Regulation (in Dutch: Algemene verordening gegevensbescherming, AVG). Only coded (pseudonymised) data—without names or directly identifying information—will be shared. In cases where it is necessary to share data with external institutions, secure transfer methods will be used. For example, data may be transmitted using secure platforms such as Zivver to ensure confidentiality during transmission. If the data are to be used for secondary scientific research, an assessment will take place to evaluate whether such use is permissible. This review will be conducted according to applicable institutional policies and may involve a data extraction committee, the head of department, or a designated data steward. The conditions for approval and the

outcome of the review will be documented in accordance with institutional governance procedures.

9.2 Amendments

Amendments are changes made to the research after local approval has been received (e.g. in Utrecht, the Netherlands, the Confirmation Quality Check). Any change that may cause the investigation to fall within the scope of the WMO is submitted to the ethical committee after a quality check by the research quality coordinator of the division. Other changes must undergo further review by the research quality coordinator of the division. Internationally, amendments are tested according to local rules.

9.3 End of study

The investigator will report the end of study date, and later, the final report date, in Vidatum. The end of the study is defined as the last study procedure of the last participant.

10. REFERENCES

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4. Proctor, E., Silmere, H., Raghavan, R., Hovmand, P., Aarons, G., Bunger, A., & Hensley, M. (2011). Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Adm Policy Ment Health (2011) 38:65–76

11. APPENDIX

Table 1; Taxonomy of implementation outcomes by Proctor et al [4]

Outcome	Definition
Acceptability	the perception among implementation stakeholders that a given treatment, service, practice, or innovation is agreeable, palatable, or satisfactory
Adoption	the intention, initial decision, or action to try or employ an innovation or evidence-based practice
Appropriateness	the perceived fit, relevance, or compatibility of the innovation or evidence based practice for a given practice setting, provider, or consumer; and/or perceived fit of the innovation to address a particular issue or problem
Feasibility	the extent to which a new treatment, or an innovation, can be successfully used or carried out within a given agency or setting
Fidelity	the degree to which an intervention was implemented as it was prescribed in the original protocol or as it was intended by the program developers
Costs	the cost impact of an implementation effort
Penetration	the integration of a practice within a service setting and its subsystems
Sustainability	the extent to which a newly implemented treatment is maintained or institutionalized within a service setting's ongoing, stable operations